EXHIBIT 1

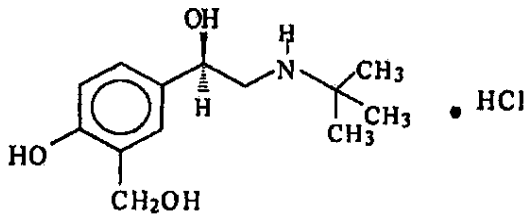
Xopenex® (levalbuterol HCl) Inhalation Solution, 0.31 mg*, 0.63 mg*, 1.25 mg*

*Potency expressed as levalbuterol

PRESCRIBING INFORMATION

DESCRIPTION:

Xopenex (levalbuterol HCl) Inhalation Solution is a sterile, clear, colorless, preservative-free solution of the hydrochloride salt of levalbuterol, the (R)-enantiomer of the drug substance racemic albuterol. Levalbuterol HCl is a relatively selective beta$_2$-adrenergic receptor agonist (see **CLINICAL PHARMACOLOGY**). The chemical name for levalbuterol HCl is (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, and its established chemical structure is as follows:



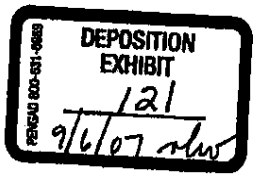
The molecular weight of levalbuterol HCl is 275.8, and its empirical formula is $C_{13}H_{21}NO_3$•HCl. It is a white to off-white, crystalline solid, with a melting point of approximately 187°C and solubility of approximately 180 mg/mL in water.

Levalbuterol HCl is the USAN modified name for (R)-albuterol HCl in the United States.

Xopenex (levalbuterol HCl) Inhalation Solution is supplied in unit-dose vials and requires no dilution before administration by nebulization. Each 3 mL unit-dose vial contains either 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl) or 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and sulfuric acid to adjust the pH to 4.0 (3.3 to 4.5).

CLINICAL PHARMACOLOGY:

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional



antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart that comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see **WARNINGS**). However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical Studies

Results from an *in vitro* study of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol. In guinea pig airways, levalbuterol HCl and racemic albuterol decreased the response to spasmogens (e.g., acetylcholine and histamine), whereas (S)-albuterol was ineffective. These results suggest that most of the bronchodilatory effect of racemic albuterol is due to the (R)-enantiomer.

Intravenous studies in rats with racemic albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics (Adults and Adolescents ≥12 years old)

The inhalation pharmacokinetics of Xopenex Inhalation Solution were investigated in a randomized cross-over study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of Xopenex Inhalation Solution and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution by nebulization using a PARI LC Jet™ nebulizer with a Dura-Neb® 2000 compressor.

Following administration of a single 1.25 mg dose of Xopenex Inhalation Solution, exposure to (R)-albuterol (AUC of 3.3 ng·hr/mL) was approximately 2-fold higher than following administration of a single 2.5 mg dose of racemic albuterol inhalation solution (AUC of 1.7 ng·hr/mL) (see **Table 1**). Following administration of a cumulative 5 mg dose of Xopenex Inhalation Solution (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic albuterol inhalation solution (2.5 mg given every 30

minutes for a total of four doses), C_{max} and AUC of (R)-albuterol were comparable (see **Table 1**).

Table 1: Mean (SD) Values for Pharmacokinetic Parameters in Healthy Adults

	Single Dose		Cumulative Dose	
	Xopenex 1.25 mg	Racemic albuterol sulfate 2.5 mg	Xopenex 5 mg	Racemic albuterol sulfate 10 mg
C_{max} (ng/mL)				
(R)-albuterol	1.1 (0.45)	0.8 (0.41)**	4.5 (2.20)	4.2 (1.51)**
T_{max} (h)[Y]				
(R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (-0.18*, 1.25)	0.2 (-0.28*, 1.00)
AUC (ng·h/mL)				
(R)-albuterol	3.3 (1.58)	1.7 (0.99)**	17.4 (8.56)	16.0 (7.12)**
$T_{\frac{1}{2}}$ (h)				
(R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

[Y] Median (Min, Max) reported for T_{max}.
* A negative T_{max} indicates C_{max} occurred between first and last nebulizations.
** Values reflect only (R)-albuterol and do not include (S)-albuterol.

Pharmacokinetics (Children 6–11 years old)

The pharmacokinetic parameters of (R)-and (S)-albuterol in children with asthma were obtained using population pharmacokinetic analysis. These data are presented in Table 2. For comparison, adult data obtained by conventional pharmacokinetic analysis from a different study are also presented in Table 2.

In children, AUC and C_{max} of (R)-albuterol following administration of 0.63 mg Xopenex Inhalation Solution were comparable to that following administration of 1.25 mg racemic albuterol sulfate inhalation solution.

Given the same dose of 0.63 mg of Xopenex to children and adults, the predicted C_{max} of (R)–albuterol in children was similar to that in adults (0.52 vs. 0.56 ng/mL), while predicted AUC in children (2.55 ng·hr/mL) was about 1.5-fold higher than that in adults (1.65 ng·hr/mL). These data support lower doses for children 6-11 years old compared to the adult doses (see **Dosage and Administration**).

Table 2: (R)-Albuterol Exposure in Adults and Pediatric Subjects (6-11 years)

	Children 6-11 years				Adults ≥12 years	
Treatment	Xopenex 0.31 mg	Xopenex 0.63 mg	Racemic albuterol 1.25mg	Racemic albuterol 2.5 mg	Xopenex 0.63 mg	Xopenex 1.25 mg
$AUC_{0-\infty}$ (ng·hr/mL) [c]	1.36	2.55	2.65	5.02	1.65 [a]	3.3 [b]
C_{max} (ng/mL) [d]	0.303	0.521	0.553	1.08	0.56 [a]	1.1 [b]

[a] The values are predicted by assuming linear pharmacokinetics
[b] The data obtained from Table 1
[c] Area under the plasma concentration curve from time 0 to infinity
[d] Maximum plasma concentration

Pharmacodynamics (Adults and Adolescents ≥12 years old)

In a randomized, double-blind, placebo-controlled, cross-over study, 20 adults with mild-to-moderate asthma received single doses of Xopenex Inhalation Solution (0.31, 0.63, and 1.25 mg) and racemic albuterol sulfate inhalation solution (2.5 mg). All doses of active treatment produced a significantly greater degree of bronchodilation (as measured by percent change from pre-dose in mean FEV_1) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator responses to 1.25 mg of Xopenex Inhalation Solution and 2.5 mg of racemic albuterol sulfate inhalation solution were clinically comparable over the 6-hour evaluation period, except for a slightly longer duration of action (>15% increase in FEV_1 from baseline) after administration of 1.25 mg of Xopenex Inhalation Solution. Systemic beta-adrenergic adverse effects were observed with all active doses and were generally dose-related for (R)-albuterol. Xopenex Inhalation Solution at a dose of 1.25 mg produced a slightly higher rate of systemic beta-adrenergic adverse effects than the 2.5 mg dose of racemic albuterol sulfate inhalation solution.

In a randomized, double-blind, placebo-controlled, cross-over study, 12 adults with mild-to-moderate asthma were challenged with inhaled methacholine chloride 20 and 180 minutes following administration of a single dose of either 2.5 mg of racemic albuterol sulfate, 1.25 mg of Xopenex, 1.25 mg of (S)-albuterol, or placebo using a PARI LC Jet™ nebulizer. Racemic albuterol sulfate, Xopenex, and (S)-albuterol had a protective effect against methacholine-induced bronchoconstriction 20 minutes after administration, although the effect of (S)-albuterol was minimal. At 180 minutes after administration, the bronchoprotective effect of 1.25 mg of Xopenex was comparable to that of 2.5 mg of racemic albuterol sulfate. At 180 minutes after administration, 1.25 mg of (S)-albuterol had no bronchoprotective effect.

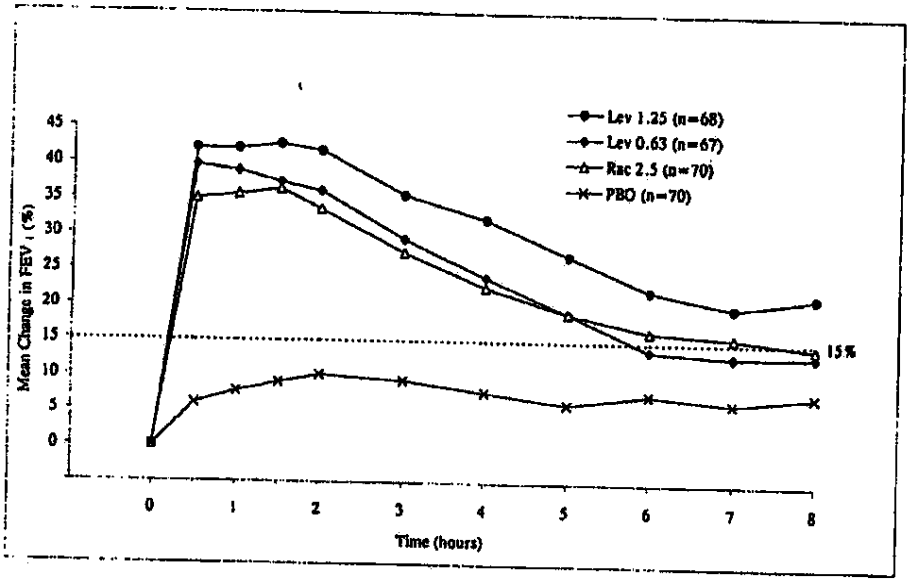
In a clinical study in adults with mild-to-moderate asthma, comparable efficacy (as measured by change from baseline in FEV_1) and safety (as measured by heart rate, blood pressure, ECG, serum potassium, and tremor) were demonstrated after a cumulative dose of 5 mg of Xopenex Inhalation Solution (four consecutive doses of 1.25 mg administered every 30 minutes) and 10 mg of racemic albuterol sulfate inhalation solution (four consecutive doses of 2.5 mg administered every 30 minutes).

Clinical Trials (Adults and Adolescents ≥12 years old)

The safety and efficacy of Xopenex Inhalation Solution were evaluated in a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study in 362 adult and adolescent patients 12 years of age and older, with mild-to-moderate asthma (mean baseline FEV_1 60% of predicted). Approximately half of the patients were also receiving inhaled corticosteroids. Patients were randomized to receive Xopenex 0.63 mg, Xopenex 1.25 mg, racemic albuterol sulfate 1.25 mg, racemic albuterol sulfate 2.5 mg, or placebo three times a day administered via a PARI LC Plus™ nebulizer and a Dura-Neb® portable compressor. Racemic albuterol delivered by a chlorofluorocarbon (CFC) metered dose inhaler (MDI) was used on an as-needed basis as the rescue medication.

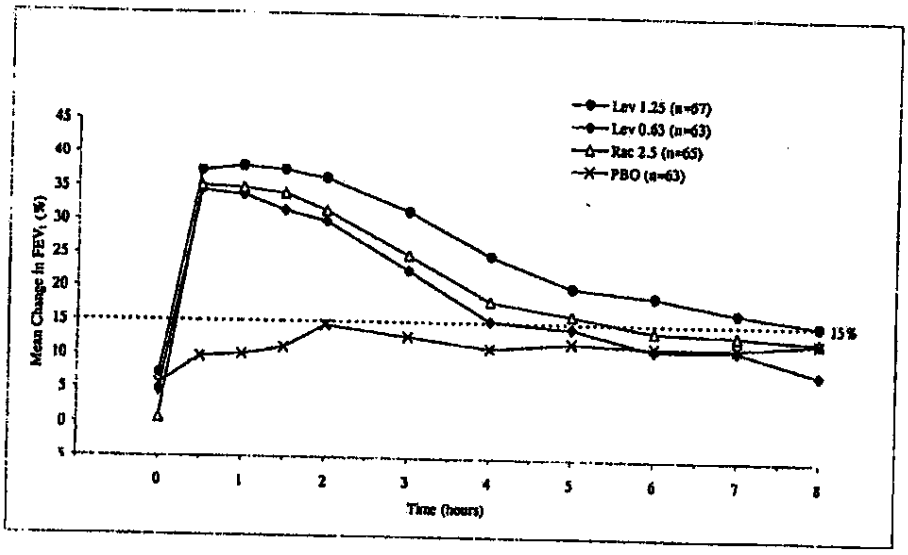
Efficacy, as measured by the mean percent change from baseline in FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 29. On both day 1 (see **Figure 1**) and day 29 (see **Figure 2**), 1.25 mg of Xopenex demonstrated the largest mean percent change from baseline in FEV_1 compared to the other active treatments. A dose of 0.63 mg of Xopenex and 2.5 mg of racemic albuterol sulfate produced a clinically comparable mean percent change from baseline in FEV_1 on both day 1 and day 29.

148 **Figure 1:** **Mean Percent Change from Baseline in FEV_1 on Day 1, Adults and**
149 **Adolescents ≥12 years old**



150

151 **Figure 2:** **Mean Percent Change from Baseline in FEV_1 on Day 29, Adults and**
152 **Adolescents ≥12 years old**



153

The mean time to onset of a 15% increase in FEV_1 over baseline for levalbuterol at doses of 0.63 mg and 1.25 mg was approximately 17 minutes and 10 minutes, respectively, and the mean time to peak effect for both doses was approximately 1.5 hours after 4 weeks of treatment. The mean duration of effect, as measured by a >15% increase from baseline in FEV_1, was approximately 5 hours after administration of 0.63 mg of levalbuterol and approximately 6 hours after administration of 1.25 mg of levalbuterol after 4 weeks of treatment. In some patients, the duration of effect was as long as 8 hours.

Clinical Trials (Children 6–11 years old)

A multi-center, randomized, double-blind, placebo- and active-controlled study was conducted in children with mild-to-moderate asthma (mean baseline FEV_1 73% of predicted) (n =316). Following a one week placebo run-in, subjects were randomized to Xopenex (0.31 or 0.63 mg), racemic albuterol (1.25 or 2.5 mg), or placebo which were delivered TID for three weeks using a PARI LC Plus™ nebulizer and a Dura-Neb® 3000 compressor.

Efficacy, as measured by mean peak percent change from baseline in FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 21. Time profile FEV_1 curves for day 1 and day 21 are shown in Figure 3 and Figure 4, respectively. The onset of effect (time to a 15% increase in FEV_1 over test day baseline) and duration of effect (maintenance of a >15% increase in FEV_1 over test day baseline) of levalbuterol were clinically comparable to those of racemic albuterol.

Figure 3: Mean Percent Change from Baseline FEV_1 on Day 1, Children 6-11 Years of Age

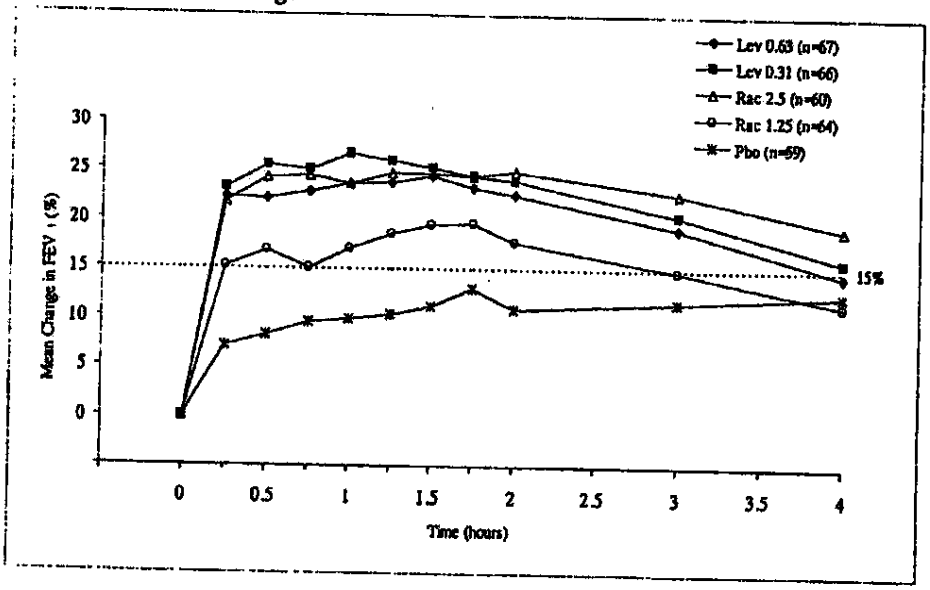
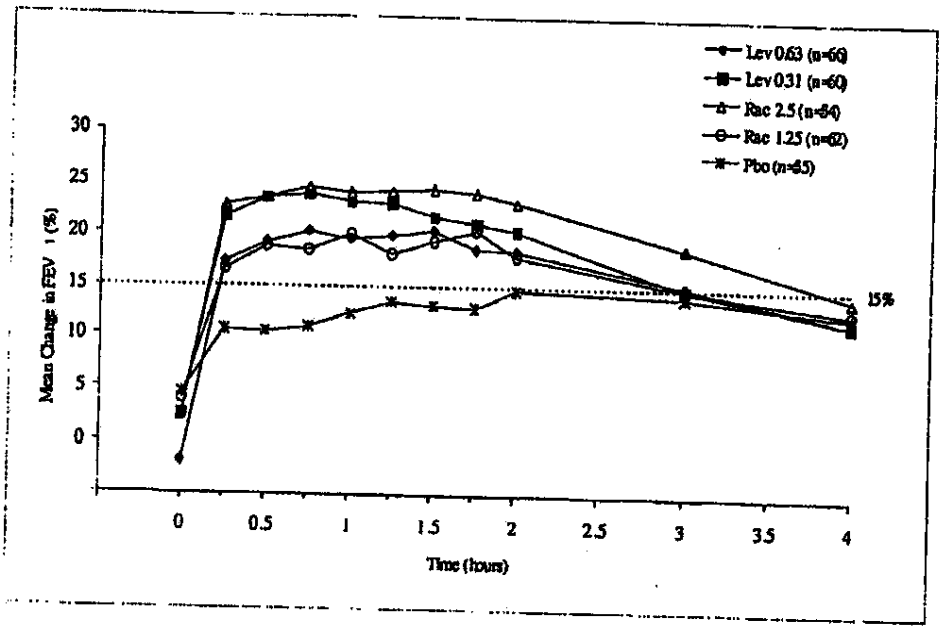


Figure 4: Mean Percent Change from Baseline FEV_1 on Day 21, Children 6-11 Years of Age



INDICATIONS AND USAGE:

Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS:

Xopenex (levalbuterol HCl) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

WARNINGS:

1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, Xopenex Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Xopenex Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Xopenex Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: Xopenex Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Xopenex Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving Xopenex Inhalation Solution.

PRECAUTIONS:

General

Levalbuterol HCl, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients

See illustrated Patient's Instructions for Use.

The action of Xopenex (levalbuterol HCl) Inhalation Solution may last up to 8 hours. Xopenex Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of dosing of Xopenex Inhalation Solution without consulting your physician. If you find that treatment with Xopenex Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are taking Xopenex Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, headache, dizziness, and tremor or nervousness. If you are pregnant or nursing, contact your physician about the use of Xopenex Inhalation Solution.

Effective and safe use of Xopenex Inhalation Solution requires consideration of the following information in addition to that provided under Patient's Instructions for Use:

Xopenex Inhalation Solution single-use low-density polyethylene (LDPE) vials should be protected from light and excessive heat. Store in the protective foil pouch between 20°C and 25°C (68°F and 77°F) [see USP Controlled Room Temperature]. Do not use after the expiration date stamped on the container. Unused vials should be stored in the protective foil pouch. Once the foil pouch is opened, the vials should be used within two weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within one week. Discard any vial if the solution is not colorless.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. Beta-blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Xopenex (levalbuterol HCl) Inhalation Solution, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no

acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

3. Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol HCl and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Xopenex Inhalation Solution.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Xopenex Inhalation Solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levalbuterol HCl on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol HCl alone. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 260 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 35 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Although levalbuterol HCl has not been tested for

clastogenicity, racemic albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

Teratogenic Effects — Pregnancy Category C

A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of Xopenex Inhalation Solution in pregnant women. Because animal reproduction studies are not always predictive of human response, Xopenex Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of Xopenex Inhalation Solution for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Levalbuterol HCl has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol HCl is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including racemic albuterol.

Nursing Mothers

Plasma levels of levalbuterol after inhalation of therapeutic doses are very low in humans, but it is not known whether levalbuterol is excreted in human milk.

Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of Xopenex Inhalation Solution by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Xopenex Inhalation Solution is administered to a nursing woman.

Pediatrics

The safety and efficacy of Xopenex (levalbuterol HCl) Inhalation Solution have been established in pediatric patients 6 years of age and older in one adequate and well-controlled clinical trial (see **CLINICAL PHARMACOLOGY; Pharmacodynamics and Clinical Trials**). Use of Xopenex in children is also supported by evidence from adequate and well-controlled studies of Xopenex in adults, considering that the pathophysiology and the drug's exposure level and effects in pediatric and adult patients are substantially similar. Safety and effectiveness of Xopenex in pediatric patients below the age of 6 years have not been established.

Geriatrics

Data on the use of Xopenex in patients 65 years of age and older are very limited. A very small number of patients 65 years of age and older were treated with Xopenex Inhalation Solution in a 4-week clinical study (see **CLINICAL PHARMACOLOGY; Clinical Trials**) (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. There are insufficient data to determine if the safety and efficacy of Xopenex Inhalation Solution are different in patients < 65 years of age and patients 65 years of age and older. In general, patients 65 years of age and older should be started at a dose of

0.63 mg of Xopenex Inhalation Solution. If clinically warranted due to insufficient bronchodilator response, the dose of Xopenex Inhalation Solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS (Adults and Adolescents ≥12 years old):

Adverse events reported in ≥2% of patients receiving Xopenex Inhalation Solution or racemic albuterol and more frequently than in patients receiving placebo in a 4-week, controlled clinical trial are listed in **Table 4.**

Table 4: Adverse Events Reported in a 4-Week, Controlled Clinical Trial in Adults and Adolescents ≥12 years old

Body System Preferred Term	Percent of Patients Placebo (n=75)	Xopenex 1.25 mg (n=73)	Xopenex 0.63 mg (n=72)	Racemic albuterol 2.5 mg (n=74)
Body as a Whole				
Allergic reaction	1.3	0	0	2.7
Flu syndrome	0	1.4	4.2	2.7
Accidental injury	0	2.7	0	0
Pain	1.3	1.4	2.8	2.7
Back pain	0	0	0	2.7
Cardiovascular System				
Tachycardia	0	2.7	2.8	2.7
Migraine	0	2.7	0	0
Digestive System				
Dyspepsia	1.3	2.7	1.4	1.4
Musculoskeletal System				
Leg cramps	1.3	2.7	0	1.4
Central Nervous System				
Dizziness	1.3	2.7	1.4	0
Hypertonia	0	0	0	2.7
Nervousness	0	9.6	2.8	8.1
Tremor	0	6.8	0	2.7
Anxiety	0	2.7	0	0
Respiratory System				
Cough increased	2.7	4.1	1.4	2.7
Infection viral	9.3	12.3	6.9	12.2
Rhinitis	2.7	2.7	11.1	6.8
Sinusitis	2.7	1.4	4.2	2.7
Turbinate edema	0	1.4	2.8	0

The incidence of certain systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was slightly less in the Xopenex 0.63 mg group as compared to the other active treatment groups. The clinical significance of these small differences is unknown.

Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium one hour after drug administration on day 1 and day 29 were clinically comparable in the Xopenex 1.25 mg and the racemic albuterol 2.5 mg groups (see **Table 5**). Changes in heart rate and plasma glucose were slightly less in the Xopenex 0.63 mg group compared to the other active treatment groups (see **Table 5**). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with day 1 in all active treatment groups.

Table 5: Mean Changes from Baseline in Heart Rate at 15 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) in Adults and Adolescents ≥12 years old

	Mean Changes (day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.63 mg, n=72	2.4	4.6	–0.2
Xopenex 1.25 mg, n=73	6.9	10.3	–0.3
Racemic albuterol 2.5 mg, n=74	5.7	8.2	–0.3
Placebo, n=75	–2.8	–0.2	–0.2

No other clinically relevant laboratory abnormalities related to administration of Xopenex Inhalation Solution were observed in this study.

In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received Xopenex 1.25 mg compared to the other active treatment groups.

The following adverse events, considered potentially related to Xopenex, occurred in less than 2% of the 292 subjects who received Xopenex and more frequently than in patients who received placebo in any clinical trial:

Body as a Whole:	chills, pain, chest pain
Cardiovascular System:	ECG abnormal, ECG change, hypertension, hypotension, syncope
Digestive System:	diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea
Hemic and Lymphatic System:	lymphadenopathy
Musculoskeletal System:	leg cramps, myalgia
Nervous System:	anxiety, hypesthesia of the hand, insomnia, paresthesia, tremor
Special Senses:	eye itch

The following events, considered potentially related to Xopenex, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

ADVERSE REACTIONS (Children 6-11 years old):

Adverse events reported in ≥2% of patients in any treatment group and more frequently than in patients receiving placebo in a 3-week, controlled clinical trial are listed in Table 6.

Table 6: Most Frequently Reported Adverse Events (≥2% in Any Treatment Group) and More Frequently Than Placebo During the Double-Blind Period (ITT Population, 6-11 Years Old)

	Percent of Patients				
Body System Preferred Term	Placebo (n=59)	Xopenex 0.31 mg (n=66)	Xopenex 0.63 mg (n=67)	Racemic albuterol 1.25 mg (n=64)	Racemic albuterol 2.5 mg (n=60)
Body as a Whole					
Abdominal pain	3.4	0	1.5	3.1	6.7
Accidental injury	3.4	6.1	4.5	3.1	5.0
Asthenia	0	3.0	3.0	1.6	1.7
Fever	5.1	9.1	3.0	1.6	6.7
Headache	8.5	7.6	11.9	9.4	3.3
Pain	3.4	3.0	1.5	4.7	6.7
Viral Infection	5.1	7.6	9.0	4.7	8.3
Digestive System					
Diarrhea	0	1.5	6.0	1.6	0
Hemic and Lymphatic					
Lymphadenopathy	0	3.0	0	1.6	0
Musculoskeletal System					
Myalgia	0	0	1.5	1.6	3.3
Respiratory System					
Asthma	5.1	9.1	9.0	6.3	10.0
Pharyngitis	6.8	3.0	10.4	0	6.7
Rhinitis	1.7	6.1	10.4	3.1	5.0
Skin and Appendages					
Eczema	0	0	0	0	3.3
Rash	0	0	7.5	1.6	0
Urticaria	0	0	3.0	0	0
Special Senses					
Otitis Media	1.7	0	0	0	3.3

Note: Subjects may have more than one adverse event per body system and preferred term.

Changes in heart rate, plasma glucose, and serum potassium are shown in Table 7. The clinical significance of these small differences is unknown.

Table 7: Mean Changes from Baseline in Heart Rate at 30 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 years old

	Mean Changes (Day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n=66	0.8	4.9	–0.31
Xopenex 0.63 mg, n=67	6.7	5.2	-0.36
Racemic albuterol 1.25 mg, n=64	6.4	8.0	–0.27
Racemic albuterol 2.5 mg, n=60	10.9	10.8	–0.56
Placebo, n=59	–1.8	0.6	–0.05
	Mean Changes (Day 21)		
	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n= 60	0	2.6	-0.32
Xopenex 0.63 mg, n=66	3.8	5.8	-0.34
Racemic albuterol 1.25 mg, n= 62	5.8	1.7	-0.18
Racemic albuterol 2.5 mg, n= 54	5.7	11.8	-0.26
Placebo, n= 55	-1.7	1.1	-0.04

OVERDOSAGE:

The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE REACTIONS**, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia also may occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of Xopenex Inhalation Solution. Treatment consists of discontinuation of Xopenex Inhalation Solution together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of Xopenex Inhalation Solution.

The intravenous median lethal dose of levalbuterol HCl in mice is approximately 66 mg/kg (approximately 70 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION:

Children 6–11 years old: The recommended dosage of Xopenex (levalbuterol HCl) Inhalation Solution for patients 6–11 years old is 0.31 mg administered three times a day, by nebulization. Routine dosing should not exceed 0.63 mg three times a day.

Adults and Adolescents ≥12 years old: The recommended starting dosage of Xopenex (levalbuterol HCl) Inhalation Solution for patients 12 years of age and older is 0.63 mg administered three times a day, every 6 to 8 hours, by nebulization.

Patients 12 years of age and older with more severe asthma or patients who do not respond adequately to a dose of 0.63 mg of Xopenex Inhalation Solution may benefit from a dosage of 1.25 mg three times a day.

Patients receiving the highest dose of Xopenex Inhalation Solution should be monitored closely for adverse systemic effects, and the risks of such effects should be balanced against the potential for improved efficacy.

The use of Xopenex Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the expected relief, medical advice should be sought immediately, since this is often a sign of seriously worsening asthma that would require reassessment of therapy.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of Xopenex Inhalation Solution have been established in clinical trials when administered using the PARI LC Jet™ and the PARI LC Plus™ nebulizers, and the PARI Master® Dura-Neb® 2000 and Dura-Neb® 3000 compressors. The safety and efficacy of Xopenex Inhalation Solution when administered using other nebulizer systems have not been established.

HOW SUPPLIED:

Xopenex (levalbuterol HCl) Inhalation Solution is supplied in 3 mL unit-dose, low-density polyethylene (LDPE) vials as a clear, colorless, sterile, preservative-free, aqueous solution in three different strengths of levalbuterol (0.31 mg, 0.63 mg, 1.25 mg). Each strength of Xopenex Inhalation Solution is available in a shelf-carton containing one or more foil pouches, each containing 12 unit-dose LDPE vials.

Xopenex (levalbuterol HCl) Inhalation Solution, 0.31 mg *(foil pouch label color green)* contains 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 63402-511-24).

Xopenex (levalbuterol HCl) Inhalation Solution, 0.63 mg *(foil pouch label color yellow)* contains 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 63402-512-24).

Xopenex (levalbuterol HCl) Inhalation Solution, 1.25 mg *(foil pouch label color red)* contains 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl) and is available in cartons of 24 unit-dose LDPE vials (NDC 63402-513-24).

CAUTION:

Federal law (U.S.) prohibits dispensing without prescription.

Store the Xopenex (levalbuterol HCl) Inhalation Solution in the protective foil pouch at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from light and excessive heat. Keep unopened vials in the foil pouch. Once the foil pouch is opened, the vials should be used within two weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within one week. Discard any vial if the solution is not colorless.

Manufactured for:
Sepracor Inc.
Marlborough, MA 01752 USA
by ALP Inc., Woodstock, IL 60098 USA
1-877-SEPRACOR
To report adverse events, call 1-888-455-8383.
For medical information, call 1-800-739-0565.

January 2002
400437-R3

PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Patient's Instructions for Use

Xopenex® (levalbuterol HCl) Inhalation Solution; 0.31 mg*, 0.63 mg*, 1.25 mg*; 3 mL Unit-Dose Vials

***Potency expressed as levalbuterol**

Read complete instructions carefully before using.

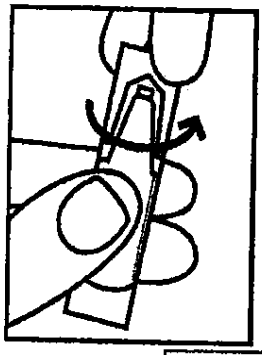


Figure 1

1. Open the foil pouch by tearing on the serrated edge along the seam of the pouch. Remove one unit-dose vial for immediate use. Keep the rest of the unused unit-dose vials in the foil pouch to protect them from light.

2. Carefully twist open the top of one unit-dose vial (**Figure 1**) and squeeze the entire contents into the nebulizer reservoir.

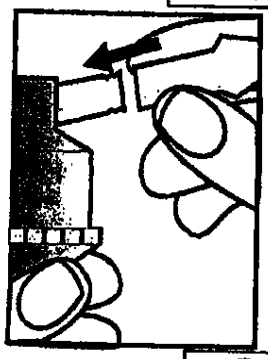


Figure 2

3. Connect the nebulizer reservoir to the mouthpiece or face mask (**Figure 2**).

4. Connect the nebulizer to the compressor.

5. Sit in a comfortable, upright position. Place the mouthpiece in your mouth (**Figure 3**) (or put on the face mask) and turn on the compressor.

6. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer reservoir (about 5 to minutes). At this point, the treatment is finished.

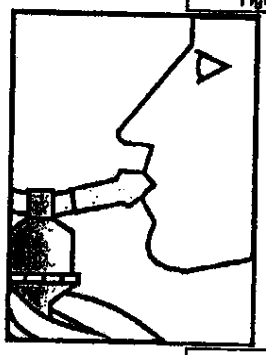


Figure 3

7. Clean the nebulizer (see manufacturer's instructions).

Note: Xopenex (levalbuterol HCl) Inhalation Solution should be used in a nebulizer only under the direction of a physician. More frequent administration or higher doses are not recommended without first discussing with your doctor. This solution should not be injected or administered orally. Protect from light and excessive heat. Store in the protective foil pouch at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Keep unopened vials in the foil pouch. Once the foil pouch is opened, the vials should be used within two weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within one week. Discard any vial if the solution is not colorless.

The safety and effectiveness of Xopenex Inhalation Solution have not been determined when one or more drugs are mixed with it in a nebulizer. Check with your doctor before mixing any medications in your nebulizer.

Manufactured for:
Sepracor Inc.
Marlborough, MA 01752 USA
by ALP Inc., Woodstock, IL 60098 USA
1-877-SEPRACOR
To report adverse events, call 1-888-455-8383.
For medical information, call 1-800-739-0565.

January 2002
400437-R3

EXHIBIT 2

REDACTED

EXHIBIT 3

PATENT SPECIFICATION (11) 1200886

1200886

NO DRAWINGS

(21) Application No. 42590/66 (22) Filed 23 Sept. 1966
(21) Application No. 18383/67 (22) Filed 21 April 1967
(23) Complete Specification filed 15 Sept. 1967
(45) Complete Specification published 5 Aug. 1970
(51) International Classification C 07 c 91/00, 103/00, 135/00
(52) Index at acceptance
C2C 172—194—284 174—198—272 183—188—289 213 215 220 225 226 227 22Y 246 250 251 25Y 29X 29Y 302 30Y 321 322 323 327 32Y 342 345 34Y 351 354 355 360 361 362 363 364 365 366 367 368 36Y 450 456 45Y 491 502 503 50Y 583 620 624 628 62X 633 650 652 65X 660 662 668 680 682 790 79Y KH LF LG LS LY

(72) Inventors LAWRENCE HENRY CHARLES LUNTS, PAUL TOON and DAVID TREVOR COLLEN

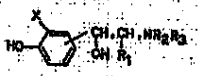
(54) PHENYLAMINOETHANOL DERIVATIVES

(71) We, ALLEN AND HANBURY'S LIMITED, a British Company of Three Colts Lane, Bethnal Green, London, E.2., England do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides compounds of the general formula:—

This invention relates to novel 1-phenyl-2-aminoethanol derivatives having biological activity, and to compositions containing the same.

The present invention provides compounds of the general formula:—



I

and physiologically acceptable acid addition salts thereof, in which:—

R_1 represents a hydrogen atom or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms;

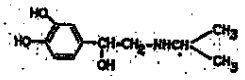
R_2 represents a hydrogen atom, or a benzyl group;

R_3 represents a hydrogen atom, or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms which radical may be substituted by hydroxyl groups, amino groups or heterocyclic rings, containing one or more heteroatoms, for example morpholino, or represents a cycloalkyl, aralkyl or aryloxyalkyl radical which radicals may optionally be substituted for example by one or more alkoxy or hydroxy groups; and

X represents a hydroxyalkyl or hydroxyaralkyl radical having a straight or branched alkyl chain containing from 1 to 6 carbon atoms, or a carboxyl radical, or an alkoxycarbonyl radical of the formula $—COOR_a$ (where R_a represents a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms), or represents a radical of the formula —CONHOH or —$CONHNH_2$, or an amido radical of the formula $—CONR_bR_c$ (where R_b and R_c, which may be the same or different, each represent a hydrogen atom or an arylalkyl radical or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms which may be substituted by hydroxyl or amino groups or where R_b and R_c together with the adjacent nitrogen atom form a heterocyclic ring which may contain additional hetero atoms).

As the compounds of general formula I possess at least one asymmetric carbon atom, the invention also includes all the possible optically active forms and racemic mixtures of the compounds. The racemic mixtures may be resolved by conventional methods, for example, by salt formation with an optically active acid, followed by fractional crystallisation. Those compounds in which the side chain substituent is para to the phenolic hydroxyl group or para to substituent X are preferred.

The compounds of the invention possess either stimulant or blocking actions on β-adrenergic receptors. Compounds which have a stimulant effect on β-adrenergic receptors are used mainly as broncho-dilators. However, known β-adrenergic stimulants, for example isoprenaline, which is 3,4-dihydroxy-α-(isopropylaminomethyl)benzyl alcohol



also affect the heart, and are potent cardiac stimulators at effective bronchodilator doses. The compounds of the invention which possess stimulant activity on β-adrenergic receptors have been found to exert a more selective effect on bronchial muscle so that bronchodilation is possible without excessive cardiac stimulation. For example, the compound α^1 - tert. - butylaminomethyl - 4 - hydroxy - *m* - xylene - $\alpha^1\alpha^3$ - diol (AH 3365) has been tested on asthmatic patients and it was found that 100 μg., doses of this compound given by aerosol, are at least equal in speed of onset and intensity of action to isoprenaline at the same dose, and it is longer acting than isoprenaline. It was also found that AH 3365 did not affect the pulse rate or blood pressure at four times the effective dose whereas isoprenaline had a marked effect on both measurements, as shown in Table I below. In contrast to isoprenaline which is poorly active when given orally, AH 3365 has been found to be an effective bronchodilator in human beings after oral administration again without obvious cardiovascular actions.

TABLE I

Changes in heart rate and pulse-pressure after administration of AH 3365 and isoprenaline by aerosol. Mean of 6 subjects.

	5 minutes		10 minutes		15 minutes		20 minutes	
	Pulse rate per min.	Pulse pressure mm. Hg.	Pulse rate per min.	Pulse pressure mm. Hg.	Pulse rate per min.	Pulse pressure mm. Hg.	Pulse rate per min.	Pulse pressure mm. Hg.
AH 3365 200 µg.	−1(±1)	−0.5(±2.1)	−5(±1)	−3(±2.9)			−6(±1)	−4(±2.2)
AH 3365 400 µg.	−2(±1)	+1.5(±2.2)	−4(±1)	−1(±1.9)			−4(±1)	−1(±1.7)
Isoprenaline 200 µg.	+19(±6)	+27.5(±9.8)	+6(±2)	+11(±2.6)	+2(±2)	+3.5(±2.3)		

Amongst the other compounds of the invention which were found to possess β-adrenergic stimulant activity are those given below:—

4 - hydroxy - α¹ - isopropylaminomethyl - m - xylene - α¹,α¹ - diol.
α¹ - (cyclopentylaminomethyl) - 4 - hydroxy - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - (1' - isopropylaminopropyl) - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - [(2 - indol - 3 - yl - 1 - methylethyl)amino]methyl - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - {[(1 - methyl - 2 - phenoxyethyl)amino]methyl} - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - {[(p - methoxy - α - methylphenethyl)amino]methyl} - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - [(p - hydroxy - α - methylphenethylamino)methyl] - m - xylene - α¹,α¹ - diol.
4 - hydroxy - α¹ - {[(1 - methyl - 2 - morpholinoethyl)amino]methyl} - m - xylene - α¹,α¹ - diol.

These compounds were tested in anaesthetised guinea pigs for the ability to relieve bronchospasm induced by the injection of acetylcholine, 5-hydroxytrytamine, bradykinin and histamine.

Other uses for the compounds of the invention which possess β-adrenergic stimulant activity may include the treatment of glaucoma, and also the control of gastric acid secretion in the treatment of peptic ulceration. The cardiovascular side-effects of known β-adrenergic stimulants limit their usefulness in these cases.

The compounds of the invention which possess blocking activities on β-adrenergic receptors are of use in the treatment or prophylaxis of cardiovascular disorders, for example, arrhythmias, coronary heart disease, angina pectoris and hypertension. Known β-adrenergic blocking agents have undesirable side effects, for example 3,4 - dichloro - α - (isopropylaminomethyl) benzyl alcohol possesses potent sympathomimetic affects, and propranolol, 1-isopropyl-amino-3-(1-naphthyloxy)-propan-2-ol affects the central nervous system. The compounds of the invention however are virtually devoid of these side effects.

For example, the compound 5 - (2 - tert. - butyl - amino - 1 - hydroxyethyl) - salicylamide, when tested in conscious dogs, was found to be slightly less active than propranolol in reducing the tachycardia produced by the intravenous injection of isoprenaline. At 0.5 mg./kg., for example, the compound given orally produced at 50—60% block of the isoprenaline response, whilst propranolol at the same dose level produced a 70—80% block, the duration of action of the two compounds being similar. However, in neuropharmacological tests, the compound was found to be remarkably non-toxic, and free from central nervous depressant activity. For example, in mice, it produced only negligible behavioural effects at doses up to 400 mg/kg. administered orally, whereas animals treated with propranolol showed signs of depression at doses of 100 mg./kg. and at 400 mg./kg. the drug caused very severe and widespread central depression.

Amongst the other compounds of the invention which were found to possess β-adrenergic blocking activity when tested for the ability to inhibit the tachycardia produced by the intravenous injection of isoprenaline in anaesthetised dogs, are to be mentioned the following:—

5-(1-hydroxy-2-isopropylaminoethyl)salicyclic acid methylester.
5-(2-amino-1-hydroxyethyl)-salicylic acid methyl ester.
5-(1-hydroxy-2-isopropylaminoethyl)-salicylamide.
5-(1-Hydroxy-2-[(1-methyl-2-phenoxyethyl)amino]ethyl)-salicylamide.
5-(1-hydroxy-2-isopropylaminoethyl)-N-methyl-salicylamide.
α²-(benzyl-tert-butylaminomethyl)-4-hydroxy-m-xylene-α¹α³-diol.
N-benzyl-5-(1-hydroxy-2-isopropylaminoethyl)salicylamide.
5-[1-hydroxy-2-(p-methoxy-α-methylphenethyl)aminoethyl]salicylic acid methyl ester.
5-[1-hydroxy-2-(isopropylamino)-butyl]salicylamide.
4[1-hydroxy-2-(isopropylamino)ethyl]salicylic acid methyl ester.

Specific preferred compounds according to the invention are those specifically referred to above.

The compounds according to the invention may be formulated for use in human or veterinary medicine for therapeutic and prophylactic purposes. They will in general be used in the form of their physiologically acceptable salts. Preferred salts include the hydrochloride, sulphate, maleate, tartrate, citrate, etc.

The invention therefore includes within its scope pharmaceutical compositions containing as active ingredients 1-phenyl-2-aminoethanol derivatives of the general formula I, or physiologically acceptable acid addition salts thereof. Such compounds may be presented for use in a conventional manner with the aid of carriers or excipients and formulatory agents as required, and with or without supplementary medicinal agents.

The compositions may include for instance solid and liquid preparations for oral use, suppositories, injections, or in a form suitable for administration by inhalation.

Oral administration is most convenient in the form of tablets which may be prepared according to conventional methods, and may be coated if required. Soluble tablets suitable for sublingual administration may also be used.

Injections may be formulated with the aid of physiologically acceptable carriers and agents as solutions, suspensions or as dry products for reconstitution before used.

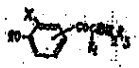
For administration by inhalation the compositions according to the invention are conveniently in the form of an aerosol spray presentation.

The dosage at which the active ingredients are administered may vary within a wide range and will depend on whether their activity is as a β-adrenergic stimulant or as a β-adrenergic blocker. A suitable oral dosage range for the stimulants is generally from 1 to 100 mg and for the blockers 50 to 1000 mg. The pharmaceutical compositions may with advantage be formulated to provide a dose within this range either as a single unit or a number of units.

In the use of an aerosol for bronchodilation the dosage unit may be determined by providing a metering valve in the aerosol pack so that it delivers a metered amount on use. Such a metered amount may be of the order of 50—1000 μg.

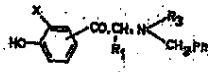
The compounds according to the invention may be prepared by a number of processes which at some stage involve the reduction of the corresponding ketone to the alcohol.

The invention therefore provides a process for the preparation of compounds of the general formula I herein which comprises reducing the carbonyl group



of a ketone of the above general formula to an alcoholic group in which X, R_1, R_2 and R_3 have the meanings given herein or are convertible thereto, if desired with protection of the phenolic hydroxyl group, the product if desired being isolated in the form of a physiologically acceptable acid addition salt.

In one method of preparation compounds of the general formula I are prepared by a process which comprises converting the methoxycarbonyl group of the ketone of general formula II (X = CO_2Me)



(II)

in which R_1 and R_2 have the meaning given above, by conventional methods to any of the other radicals represented by X in formula I, either directly, or after reduction of the carbonyl group to the alcohol with suitable hydrides for example sodium borohydride, or lithium aluminium hydride. If desired the N-benzyl group may then be removed by catalytic hydrogenolysis. Alternatively reduction of the carbonyl group and removal of the N-benzyl group can be effected in one stage by hydrogen and a noble metal catalyst. In some reactions, it may be advantageous to protect the phenol group e.g. as a benzyl ether or an acetate. The protecting group may be removed by hydrogenolysis or hydrolysis to give the required product. Compounds in which R_2 and R_3 both represent hydrogen atoms may be prepared from the dibenzyl amino compound by catalytic hydrogenation.

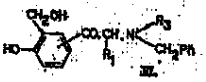
The dibenzyl compound or the primary amine may be reductively alkylated to compounds of formula I with aldehydes or ketones in the presence of hydrogen and a noble metal catalyst.

Another subsequent conversion envisaged by the invention is the reaction of the group COOMe to a tertiary alcohol by reaction with a Grignard reagent.

The 1-phenyl-2-aminoethanol derivatives of the general formula I in which X is an alkoxycarbonyl radical of the general formula —$COOR_4$, where R_4 has the meaning given above may be prepared by reacting the ketone of formula II (X = CO_2H) with an alcohol of the general formula R_4OH, in the presence of an acid catalyst, followed by catalytic hydrogenolysis to give the 1-phenyl-2-aminoethanol derivative.

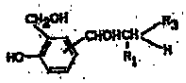
Compounds of the general formula (I) in which X is a hydroxymethyl radical may be prepared by several processes.

In the first of these processes a compound of the general formula III, or a salt thereof.



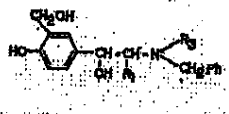
(in which R_1 and R_2 are as above defined and Ph is a phenyl radical).

is subjected to catalytic hydrogenation, preferably using a palladium oxide on charcoal catalyst to yield a compound of the general formula IV



IV

Alternatively, the ketone of formula III may be reduced with sodium borohydride to give the alcohol of general formula V and this latter may also be obtained by reduction of a compound of formula II (where X = alkoxycarbonyl) by the use of lithium aluminium hydride.

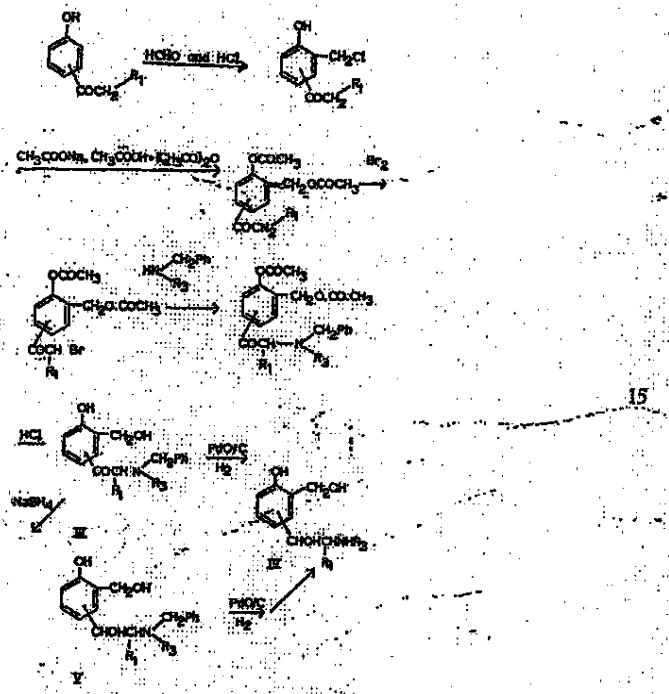


V

If desired this compound is then subjected to catalytic hydrogenation to remove the N-benzyl group, to produce a compound of formula IV.

Use of the alcohol (V) in the hydrogenation instead of the ketone III minimises the side reaction in which the $-CH_2OH$ group is reduced to a $-CH_3$ group.

The complete synthesis of the compounds starting from aryl ketones is shown in the following reaction scheme



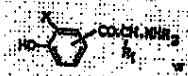
The ketone of the general formula III can be prepared from the compound (VII, X = $-CH_2OH$) below in which the hydroxy groups can be protected by acetylation, by condensation with an amine of the general formula R_2R_3NH (where R_2 and R_3 have the meanings given above) and removal of protecting groups where these are present.

The compounds of formula I in which X is a carboxyl group may be prepared by hydrolysis of the ester group of the ketone II ($X=CO_2Me$), for example with an acid catalyst, followed by catalytic hydrogenolysis to the 1-phenyl-2-aminoethanol derivative.

Compounds of formula I in which X is an amide group of the general formula $-CONR_5R_6$, where R_5 and R_6 have the meanings given above, may be prepared by reacting the ketone II ($X=CO_2R_4$) or the alcohol derived from it by reduction with an amine of the general formula R_5R_6NH, where R_5, R_6 and R_4 have the meanings given above, followed by catalytic hydrogenolysis.

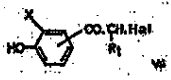
Compounds of the general formula I in which X is a $-CONHOH$ or $CONHNH_2$ radical may be prepared from the ketone of formula II ($X=CO_2R_4$) by reducing it to the alcohol of general formula I ($X=CO_2R_4$) in which R_4 has the meaning given above, and reacting this compound with hydroxylamine, NH_2OH or hydrazine NH_2NH_2 and removing the N-benzyl group to give the required product.

In an alternative process for the preparation of the 1-phenyl-2-aminoethanol derivatives of the invention, the secondary amine of the general formula VI ($X=CO_2Me$) may be used in place of the ketone II, or alcohol I ($X=CO_2Me$), for the reactions given above in which the methoxycarbonyl group is converted to any of the other radicals represented by X in the general formula I



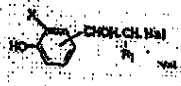
VI

The ketone of general formula II may be prepared by the condensation of an amine $R_4NH.CH_2Ph$ with a halogen derivative of general formula VII



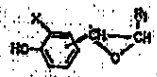
VII

The 1-phenyl-2-aminoethanol derivative of the general formula I may also be prepared by the condensation of an amine of the general formula R_5R_6NH with a halohydrin of the general formula VIII



VIII

In a further process the compounds of formula I may also be prepared by the reaction of an amine of the general formula R_5R_6NH with an epoxide of general formula IX



IX

In all of the above processes the phenolic group may be protected, e.g. as the benzyl ether.

In these formulae, R_1, R_2, R_3 and X have the meanings given above.

Compounds of the general formula I in which X is a secondary or tertiary alcoholic group may be prepared via conversion of a compound of the formula I in which in the X substituent position there is a halogen atom to an organometallic compound and reaction thereof with an aldehyde or ketone.

The following Examples illustrate the invention.

EXAMPLE 1

Preparation of 5-(1-hydroxy-2-isopropylaminoethyl) salicylamide hydrochloride

a) 5-(N-benzyl-N-isopropylglycyl)-salicylic acid methylester hydrochloride

7.3G of N-benzylisopropylamine were added to a stirred solution of 7.5 g of 5-bromoacetyl salicylic acid methyl ester in 100 ml of methyl ethyl ketone. A colourless crystalline precipitate was observed at once but stirring and refluxing was continued for 2.5 hr. After being allowed to stand at room temperature for 2 days the solvent was evaporated under reduced pressure and dry ether was added to the residual oil. The ethereal solution obtained was treated with dry hydrogen chloride gas to give 6g of the hydrochloride as an oily solid. Recrystallisation from methanol/ethyl acetate gave 3.55g of the hydrochloride as a colourless powder, m.p. 168—170°C.

b) 5-(N-Benzyl-N-isopropylglycyl)-salicylamide hydrochloride.

A solution of 15g of 5 - (N - benzyl - N - isopropyl glycyl)salicylic acid methyl ester hydrochloride in 125ml of methanol and 125ml of 0.880 ammonia solution was allowed to stand in a stoppered flask. After six days, the solution was evaporated to dryness and the residue was extracted three times, each time with 150ml of ether. The free base began to precipitate from the ethereal solution. Treatment of the mixture with hydrogen chloride gas gave a white oily material, which on boiling with ethyl acetate gave 12.5g of a white solid. Recrystallisation from methanol gave 11.0g of the amide hydrochloride as colourless crystals, m.p. 217—220°, after drying at 70° *in vacuo* to constant weight.

c) 5-(1-Hydroxy-2-isopropylaminoethyl)-salicylamide hydrochloride.

4.15G. of 5 - (N - benzyl - N - isopropyl glycyl) salicylamide hydrochloride in 250ml of methanol were hydrogenated at room temperature and pressure in the presence of 1g of a 10% palladium oxide on charcoal catalyst. Uptake of hydrogen ceased after 40 minutes. The solution was filtered and evaporated to dryness. The residue was recrystallised from methanol/ethyl acetate to give 2.3g of the product, m.p. 207—8°C.

EXAMPLE 2

Preparation of 5-[2-(N-benzyl-N-isopropylamino)-1-hydroxyethyl]salicylamide.

1.3G of 5 - (N - benzyl - N - isopropyl glycyl)salicylamide were dissolved in 50 ml. of tetrahydrofuran, then added to a stirred solution of 1.0g of lithium aluminium hydride in 250ml of tetrahydrofuran and heated under reflux for 3 hours. After cooling, water was added to decompose the excess hydride and the mixture was acidified with dilute hydrochloric acid. The solution was evaporated almost to dryness and the pH was adjusted to 8—9. Extraction with ether and ethyl acetate afforded 0.9g of a pale yellow gum.

Chromatography on silica gel and elution with cyclohexane ethyl acetate (1:1) gave 0.31 g of crystalline solid, m.p. 142.5—144.5. Recrystallisation from ether/petrol provided pure 5 - (2 - N - benzyl - N - isopropylamino-1-hydroxyethyl) salicylamide, m.p. 140—142°.

EXAMPLE 3

Preparation of N-hexyl-5-[1-hydroxy-2-isopropylaminoethyl] salicylamide hydrochloride

a) 5-(1-Hydroxy-2-isopropylaminoethyl)-salicylic acid methylester hydrochloride

3.0g of 5 - (N - benzyl - N - isopropylglycyl) - salicylic acid methylester hydrochloride in 50ml of ethanol were hydrogenated with 0.525g of 10% palladium oxide catalyst. Hydrogen uptake was complete after 95 minutes. The solution, after removal of the catalyst was evaporated to dryness under reduced pressure to give 2.3g of a pale pink solid. Crystallisation from methanol/ethyl acetate gave 2.03g of colourless needles, m.p. 153—155°C.

b) N-Hexyl-5-(1-Hydroxy-2-isopropylaminoethyl)-salicylamide, hydrochloride

2.0G of the methyl ester of 5 - (1 - hydroxyethyl - 2 - isopropylamino) salicylic acid were dissolved in 10ml of ethanol containing 10ml of n-hexylamine and the solution was allowed to stand at room temperature. After 4 days all the ester had reacted and the solution was evaporated to dryness. Trituration with ethyl acetate containing a drop of methanol afforded 3.0g of crystalline solid, m.p. 134—144°. Recrystallisation from ethyl acetate/ether containing one drop of ethanol gave N-hexyl-5-(1-hydroxy-2-isopropylaminoethyl) salicylamide as a white powder, m.p. 134—135°.

The hydrochloride was prepared by treating 1.8g of the above base in ethyl acetate with a solution of hydrogen chloride in ether and recrystallising the product from methanol/ethyl acetate (9:1), 1.1G of the N - hexyl - 5 - (1 - hydroxyethyl - 2 - isopropylamino) salicylamide, hydrochloride separated as colourless plates, m.p. 199°.

EXAMPLE 4

Preparation of 5-(2-tert-butylamino-1-hydroxyethyl) salicylamide hydrochloride

1.0G of 5 - (N - benzyl - N - tert - butylglycyl)salicylamide hydrochloride, 0.2g of 10% palladium oxide on charcoal catalyst, 20ml of ethanol and 15ml of water were shaken at room temperature in an atmosphere of hydrogen until uptake of hydrogen ceased. The catalyst was filtered off and the solvent was removed by distillation. The residue was crystallised from methanol/isopropyl acetate to give 0.56 g of a pale pink solid, m.p. 203—4°.

EXAMPLE 5

Preparation of N-benzyl-5-(1-hydroxy-2-isopropylaminoethyl)-salicylamide, hydrochloride

8.0G of 5 - (1 - hydroxy - 2 - isopropylaminoethyl) - salicylic acid, methyl ester were dissolved in 40ml of ethanol containing 40ml of benzylamine. The solution was allowed to stand at room temperature for 4 days before evaporation to a small volume under reduced pressure. The gummy residue was treated with 50ml of dilute hydrochloric acid and the white solid was filtered off and recrystallised from methanol/ethyl acetate to afford 5.05g of N - benzyl - 5 - (1 - hydroxy - 2 - isopropylaminoethyl) - salicylamide, hydrochloride, m.p. 208—209°.

EXAMPLE 6

Preparation of 5-(1-hydroxy-2-isopropylaminoethyl)-N-methyl salicylamide hydrochloride

a) 5-(N-Benzyl-N-Isopropyl-glycyl)-N-methyl-salicylamide, hydrochloride

2.5G of 5 - (N - benzyl - N - isopropyl - glycyl)salicylic acid methyl ester, hydrochloride were dissolved in 50ml of a 30% solution of methylamine in ethanol. The solution was left overnight and was then evaporated to dryness under reduced pressure. The residue was dissolved in dilute hydrochloric acid and washed with ethyl acetate, and the aqueous layer made alkaline with sodium carbonate solution to pH 8 and again extracted with ethyl acetate. The latter organic extracts were dried over sodium sulphate, concentrated and treated with an ethereal solution of hydrogen chloride to afford 1.6g of 5 - (N - benzyl - N - isopropylglycyl) - N - methyl - salicylamide, hydrochloride, m.p. 200—205°. Recrystallisation from ethyl acetate/ethanol gave rosettes, m.p. 205—209°.

b) 5-(1-Hydroxy-2-isopropylaminoethyl)-N-methyl salicylamide hydrochloride

4.2G of 5 - (N - benzyl - N - isopropylglycyl) - N - methyl salicylamide, hydrochloride were dissolved in 35 ml of 90% aqueous methanol and this solution was added to a pre-reduced suspension of 1g of 10% palladium on carbon catalyst in 15 ml of methanol.

The hydrogenation was stopped when 550ml of hydrogen had been absorbed. The catalyst was filtered off and the solution was concentrated to ca. 10ml and allowed to crystallise, affording 2.3g of 5 - (1 - hydroxy - 2 - isopropylaminoethyl) - N - methyl salicylamide hydrochloride. Recrystallisation from ethanol gave fine colourless needles, m.p. 208—209°C.

EXAMPLE 7

Preparation of 4-[1-hydroxy-2-(isopropylamino)ethyl] salicylamide

a) 4-[2-Benzylisopropylamino-1-hydroxyethyl] salicylamide

A solution of 3.55g of 4 - [2 - benzylisopropylamino - 1 - hydroxyethyl] salicylic acid, methyl ester, hydrochloride in hot water was basified with sodium bicarbonate solution and the resulting suspension was extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated, and the gummy residue dissolved in 50ml of ethanol. To this solution was added 30ml of 0.880 ammonia solution, and the resulting mixture was allowed to stand at room temperature for one week. The solution was then evaporated to dryness and the residue extracted with ether. The ether solution was evaporated to dryness, giving a whitish solid residue which was crystallised from benzene to give 1.53g of the product, m.p. 155—6°C.

b) 4-[1-Hydroxy-2-(isopropylamino)ethyl] salicylamide

A solution of 0.456g of 4 - [2 - benzylisopropylamino - 1 - hydroxyethyl] salicylamide in methanol was hydrogenated over 0.1g of pre-reduced 10% palladium on carbon catalyst. Uptake of hydrogen was complete in 19 mins. After filtering off the catalyst, the methanol solution was evaporated to dryness, leaving a glassy residue which was allowed to crystallise from a mixture of ether and ethyl acetate. This gave 0.236g of white prisms, m.p. 114—6°. From the analysis, infra-red spectrum, and equivalent weight the compound was found to contain 0.5 mole of ethyl acetate of crystallisation.

The benzoate derivative (prepared from a solution of the base in tetrahydrofuran and benzoic acid in ether) crystallised from isopropanol in small white prisms, m.p. 146—152°.

EXAMPLE 8

Preparation of 5-[1-hydroxy-2-(isopropylamino)-butyl] salicylamide, hydrochloride

a) 5-[(α-Isopropylamino)-butyryl]-salicylamide, hydrochloride

A solution of 3.0g of 5 - [(α - isopropylamino) - butyryl] - salicylic acid methyl ester hydrochloride in 50ml of ethanol and 0.880 ammonia was allowed to stand for 7 days at room temperature in a stoppered flask. The solution was evaporated to small bulk and the yellowish solid was filtered off. This was very insoluble in ether. The hydrochloride was prepared by dissolving the amide in ethanol and acidifying with dry hydrogen chloride gas to pH 4—6. The solvent was evaporated off and the off-white solid residue was crystallised from ethanol to yield 2g of a white solid, m.p. 300°.

b) 5-[1-Hydroxy-2-(isopropylamino)-butyl]salicylamide, hydrochloride

1.5G of 5 - [α - isopropylamino)butyryl] - salicylamide hydrochloride in 175 ml of methanol were hydrogenated at room temperature and pressure in the presence of 10% palladium oxide on carbon catalyst for 10 hours. The solution was filtered and evaporated to dryness. The white solid residue recrystallised from methanol/ethyl acetate as pale pink prisms containing 0.5 mole of ethyl acetate of crystallisation. The material was further crystallised from methanol/ether to give 1.0g of pale pink microcrystals containing no solvent of crystallisation, m.p. 220—221°.

EXAMPLE 9

Preparation of 5-(2-tert-butylamino-1-hydroxy-ethyl)-N-[2-(dimethylamino) ethyl] salicylamide, dihydrogen maleate

5.0G of 5 - (2 - *tert* - butylamino - 1 - hydroxyethyl) salicylic acid methyl ester were dissolved in 25ml of dimethylaminoethylamine and allowed to stand at room temperature. After 24 hours, the solution was evaporated to dryness and the residue crystallised from ethyl acetate to afford 5.0g of a cream solid, m.p. 146—51°. This base was not purified further but a portion of 2g was dissolved in 50ml of tetrahydrofuran and treated with a solution of 1.5 g of maleic acid in 10 ml of tetrahydrofuran. A white solid separated out which on recrystallisation from 95% ethanol gave 2.6g of 5 - (2 - tert - butylamino - 1 - hydroxy - ethyl)-N 1 [2 - (dimethylamino) ethyl] salicylamide, dihydrogen maleate, m.p. 199—200°.

EXAMPLE 10

Preparation of 5-[1-hydroxy-2-(isopropylamino)ethyl]-N-(2-hydroxyethyl) salicylamide, hydrate

a) 5-[(N-Benzyl, N-isopropyl)glycyl]-2-benzyloxybenzoic acid, methyl ester, hydrochloride

A solution of 2.33g of 2 - benzyloxy - 5 - bromoacetylbenzoic acid, methyl ester and 1.935g of N - benzylisopropylamine in 40 ml of methyl ethyl ketone was stirred under reflux for 5 hours, and then allowed to stand at room temperature overnight. Benzylisopropylamine hydrobromide crystallised out and was filtered off. The filtrate was evaporated to dryness, dissolved in ether and washed with water. The ether layer was then shaken with dilute HCl to produce a gum, which was extracted from the aqueous layer with chloroform. The chloroform solution was washed with brine, dried and evaporated, giving a gummy residue. When this was triturated with boiling acetone/ether 2.0g of a white solid was obtained, m.p. 160—162°.

b) 5-{2-[(N-Benzyl, N-isopropyl)amino]-1-hydroxyethyl}-2-benzyloxybenzoic acid, methyl ester, hydrochloride, hemihydrate

4.5G of 5 - [(N - benzyl, N - isopropyl)glycyl] - 2 - benzyloxybenzoic acid, methyl ester, hydrochloride was dissolved in 90ml of ethanol and to the stirred solution was added 0.9g of sodium borohydride in small portions over 30 minutes, with stirring. The resulting suspension was stirred at room temperature for a further hour, and was then evaporated to dryness and the residue shaken with ether and filtered. The filtrate when treated with ethereal hydrochloric acid, gave 4.2g of a white solid, m.p. 120—30°. Crystallisation from ethyl acetate raised the m.p. to 134—136°.

c) 5-[1-Hydroxy-2-(isopropylamino)ethyl]N-2-hydroxyethyl salicylamide, hydrate

10G of 5 - [2 - benzylisopropylamino - 1 - hydroxyethyl] - 2 - benzyloxybenzoic acid, methyl ester, hydrochloride, hemihydrate was basified to give 9.05g of white crystals. This was dissolved in a mixture of 100ml of ethanol and 40 ml of ethanolamine and left to stand at room temperature for 2 weeks. The solution was then hydrogenated over 1.0g of 10% pre-reduced palladium on carbon catalyst. Uptake of hydrogen was complete in 2.5 hours. The catalyst was filtered off and the solvents were evaporated, leaving a white solid. This was crystallised from ethyl acetate/methanol, to give 5.2g of white micro-crystals, m.p. 152—3°.

The hydrochloride of this product, m.p. 195°, was crystallised from isopropanol.

EXAMPLE 11

Preparation of 5-[1-hydroxy-2-(isopropylamino)ethyl] salicylhydroxamic acid

a) α-[(Benzylisopropylamino)methyl]-6-benzyloxy-α-hydroxy-m-toluhydroxamic acid

4.0G of 5 - {2 - [benzylisopropylamino] - 1 - hydroxyethyl} 2 - benzyloxy - benzoic acid, methyl ester, hydrochloride, hemihydrate, in 30ml of methanol was added to hydroxylamine solution prepared by mixing a solution of 16.3g of hydroxylamine hydrochloride in 110ml of methanol with a solution of 5.5g of sodium in 50ml of methanol, and filtering the precipitated NaCl.

After 1 month standing in a stoppered vessel at room temperature, the solution was evaporated, and the oily residue was extracted with ether (3 × 150ml). Evaporation of the ether gave an oil which was dissolved in a large volume (*ca* 300ml) of cyclohexane. On cooling, an oil precipitated and solidified within two days to give 2.2g of a white solid.

Recrystallisation from cyclohexane gave white crystals of the hydroxamic acid, m.p. 138—140°.

b) 5-[1-Hydroxy-2-(isopropylamino)ethyl] salicylhydroxamic acid

1.45G of α - [(benzylisopropylamino)methyl] - 6 - benzyloxy - α - hydroxy - m - toluhydroxamic acid in 32ml of methanol was hydrogenated in the presence of 0.4G of pre-reduced 10% palladium oxide on carbon catalyst suspended in 8ml of water. Hydrogenation was completed after 15 minutes. The solution was filtered and evaporated to yield a white solid. Further material was obtained by extracting the catalyst residues with 75ml of hot water. The solids were combined and triturated with tetrahydrofuran, followed by ethanol, to yield 0.46g of the product as a white solid, m.p. 186—188°.

EXAMPLE 12

Preparation of 5-(2-tert-butylamino-1-hydroxyethyl) salicylic acid hydrazide

5.0G of 5 - (2 - tert - butylamino - 1 - hydroxyethyl)salicylic acid, methyl ester was dissolved in a solution of 30ml of hydrazine hydrate in 20ml of ethanol and allowed to stand overnight at room temperature. The solution was evaporated to dryness and the brown residue triturated with ethanol/tetrahydrofuran to give 4g of a cream solid which did not melt but gradually decomposed with charring above 300°.

EXAMPLE 13

Preparation of 5-(2-benzylisopropylamino-1-hydroxyethyl)-salicylic acid methyl ester hydrochloride

12.0G of 5 - (N - benzyl - N - isopropyl glycyl) - salicylic acid methyl ester hydrochloride in 230ml of ethanol were treated with 2.404g of sodium borohydride, added portionwise over 30 mins. at room temperature. The mixture was allowed to

stand overnight. Reduction was shown to be complete by the disappearance of the band at 278 mμ in the u.v. spectrum. The mixture was then evaporated to dryness under reduced pressure at 40°; and the residue was extracted with ether (3 × 100 ml). The ether extracts were dried over $MgSO_4$, and treated with hydrogen chloride gas. The precipitated white oily material gave 6.8g of a white solid on boiling with ethyl acetate. Recrystallisation from acetone/ether gave 5.5g of the ester hydrochloride as colourless microcrystals.

EXAMPLE 14

Preparation of 4-hydroxy-α^1-isopropylaminomethyl-m-xylene-α^1,α^3 diol

a) α^1-Benzylisopropylaminomethyl-4-hydroxy-m-xylene-α^1,α^3 diol

22.0G of 5 - (N - benzyl - N - isopropylglycyl)salicylic acid methyl ester hydrochloride were basified with aqueous sodium bicarbonate solution and extracted into ether. After drying over sodium sulphate, the solution was evaporated to dryness and the residue was dissolved in 150ml of tetrahydrofuran. This solution was added dropwise to 4g of lithium aluminium hydride in 300ml of tetrahydrofuran. An insoluble complex formed. The mixture was refluxed for 7 hours under nitrogen, cooled, treated with 10 ml of water and filtered. The solid together with the residue from evaporation of the filtrate was dissolved in dilute hydrochloric acid, and this solution was basified with aqueous sodium bicarbonate solution, and continuously extracted with ether to give the free base as a gum. Crystallisation from ether/petrol gave α - benzylisopropylamino - methyl - 4 - hydroxy - m - xylene - α^1,α^3 diol as white crystals, m.p. 115—6°.

b) 4-Hydroxy-α^1-isopropylaminomethyl-m-xylene-α^1,α^3 diol

5.4G of α^1 - benzylisopropylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 diol in 100ml of ethanol and 10ml of water were hydrogenated at room temperature and pressure in the presence of 1.2g of a 10% palladium oxide on charcoal catalyst, until the uptake of hydrogen slowed markedly. The solution was filtered and evaporated to dryness. The oily residue solidified on being allowed to stand in 25ml of ethyl acetate to give 3.55g of the crystalline hydroxy diol, m.p. 139—140°. Purification by precipitation from a solution of tetrahydrofuran with ether raised the melting point to 143—45°C.

EXAMPLE 15

Preparation of 4[1-hydroxy-2-(isopropylamino)ethyl]salicylic acid, methyl ester, hydrochloride

a) 4-[2-Benzylisopropylamino-1-hydroxyethyl]salicylic acid, methyl ester, hydrochloride

2.7G of 4 - (bromoacetyl)salicylic acid, methyl ester were dissolved in 7.5ml of dry tetrahydrofuran and added at room temperature to a solution of 2.94g of N-benzylisopropylamine in 7.5ml of dry tetrahydrofuran. The resulting mixture was left to stand for 4 hours. After this time the crystals of N-benzylisopropylamine hydrobromide were filtered off and the filtrate was treated with a solution of 0.6g of sodium borohydride in 15ml of 90% ethanol. The resulting mixture was allowed to stand at room temperature for 3 days. The mixture was then evaporated to dryness, the residue was partitioned between ether and water, and the ether solution was dried and evaporated. The liquid residue was dissolved in 60ml of dry ether/ethyl acetate (1:1). This gave, on scratching with a glass rod, 2.4g of a white solid, m.p. 150—d60°. Crystallisation from ethyl acetate/methanol gave 1.615g of the product, m.p. 174—175.5°.

b) 4[1-Hydroxy-2-(isopropylamino)ethyl]salicylic acid, methyl ester, hydrochloride

A solution of 1.0g of 4 - [2 - (N - benzyl, N - isopropyl)amino - 1 - hydroxyethyl] salicylic acid, methyl ester, hydrochloride in 50ml of ethanol was hydrogenated over 0.2g of pre-reduced 10% palladium oxide on charcoal catalyst. The volume of hydrogen absorbed in 10 minutes was 60ml. The catalyst was then filtered off and the filtrate evaporated to dryness. Trituration of the residue with ethyl acetate/ether gave 0.68g of a white solid, m.p. 166—8°. Crystallisation from ethyl methyl ketone gave 0.31g of the product as large white crystals, m.p. 171.5—173°C.

EXAMPLE 16

Preparation of α^1-*tert*-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

a) α^1-Benzyl-tert-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

3.0G of 5 - (N - benzyl - N - *tert* - butyl - glycyl) - salicylic acid methyl ester hydrochloride in 40ml of water was basified with sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$ and evaporated and the basic residue in 20ml of dry tetrahydrofuran was added with stirring to 1.0g of lithium aluminium hydride in 100ml of dry tetrahydrofuran, over a period of 5 minutes. The light gelatinous precipitate that formed was stirred and refluxed for 8 hours after which time 7ml of water was carefully added and the solvents were removed under reduced pressure.

The residue was acidified with dilute hydrochloric acid and brought to pH8 with sodium hydroxide and sodium bicarbonate. The mixture was filtered and the filtrate and orange solid were separately extracted with chloroform. The combined, dried, chloroform solutions were evaporated to give 2.2g of the crude basic triol as an orange solid, when triturated with ether. A portion of the material was recrystallised from ether/light petroleum (b.p. 40—60°) to give a white solid, m.p. 109—110°C.

In an alternative process, sodium borohydride was used as the reducing agent, as follows:—

3.6G of 2 - (benzyltert-butylamino) - 4' - hydroxy - 3' - hydroxymethyl acetophenone. hydrochloride was shaken with 100ml of 10% sodium carbonate solution and 100ml of ethyl acetate. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*.

The residual gum was dissolved in 360 ml of ethanol and cooled to 15° in an ice/water bath. 8G of sodium borohydride was then added in portions over 30 mins. whilst maintaining the temperature at 15—20°. After a further 30 mins. at 20° the solution was stirred at room temperature for 2 hours. The solution was again cooled in ice and 250ml of 2N sulphuric acid were slowly added, then the solution was evaporated in vacuo until the ethanol had been removed. The clear aqueous solution was then treated with 250ml of 10% sodium carbonate solution and the oil which precipitated was extracted into ethyl acetate. The ethyl acetate layer was washed with sodium carbonate solution, then with water, and was dried over anhydrous sodium sulphate and evaporated *in vacuo*, to a small volume. Petroleum ether (b.p. 40—60°) was added, and after standing overnight a white solid was obtained. This was filtered off to give 23g of the product, m.p. 110—114°.

b) α^1-*tert*-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

0.8G of α^1 - benzyl - *tert* - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol in 20 ml of ethanol and 2ml of water was shaken with hydrogen in presence of 0.50g of pre-reduced 10% palladium on charcoal catalyst. When uptake of hydrogen was complete, the solution was filtered and evaporated under reduced pressure to give 0.4g of the base as a colourless oil which yielded a white solid m.p. 144—145° when triturated with ether/cyclohexane. Recrystallisation from ethyl acetate-cyclohexane gave a white solid, m.p. 147—149°.

An alternative process for preparing the compound of Example 16 described below:—

a) Preparation of 3-(chloromethyl)-4-hydroxy-acetophenone

500G of *p*-hydroxy-acetophenone, 1 litre of formaldehyde solution (40% w/v) and 2 litres of concentrated hydrochloric acid were stirred and cooled to 20°C. when 320g of hydrogen chloride gas was passed into the suspension whilst maintaining the temperature at 20°C. After stirring for a further 2 hrs. the mixture was allowed to stand for 18 hrs. 5 Litres of distilled water were then added and the solid was removed by filtration, washed with hot water and hot benzene to give 488G of a pale red solid m.p. 164°C. (Ref.Gazz.Chim.,Acta., *81*, 773—781. Chem.Ab., *46*, 8048 (1952) m.p. 160°C).

An alternative process for the preparation of this compound, avoiding the use of gaseous hydrogen chloride, was carried out as follows:—

3-Chloromethyl-4-hydroxyacetophenone

10Kg of *p* - hydroxy - acetophenone were added to a stirred solution of 6.6 litres of 40% w/v formaldehyde solution and 45 litres of concentrated hydrochloric acid (35—38% w/v) which had previously been heated to 45—50°. The temperature was maintained at 50° for two hours after which 45 litres of water were added. The red solid which formed was washed with 20 litres of hot water and dried at 60° in air to give 12 kg of the product as a red solid m.p. 164°.

b) Preparation of 3-(hydroxymethyl)-4-hydroxy-acetophenone diacetate

470G of 3 - (chloromethyl) - 4 - hydroxy - acetophenone, 235g of anhydrous sodium acetate, 1100 ml of glacial acetic and 550 ml of acetic anhydride were stirred and refluxed for 2 hours. The acetic acid was then distilled *in vacuo* and the residue poured into water. The oil which separated was extracted into chloroform and the chloroform evaporated *in vacuo*. The residue was distilled to yield 550 G. of a colourless oil b.p. 150—160°C/0.3 mm. $n_D^{25} = 1.517$. This oil solidified to give a white solid, m.p. 50°C.

c) Preparation of 3-(hydroxymethyl)-4-hydroxy-ω-bromoacetophenone diacetate

555G of 3 - (hydroxymethyl) - 4 - hydroxy - acetophenone diacetate and 2 litres of chloroform were stirred and cooled to 20°C. A solution of 188 ml of bromine dissolved in 400ml of chloroform was added over 1 hr, maintaining the temperature at 20°C. After the addition, 3 litres of ice/water was added and the chloroform layer was separated, washed with water and dried over sodium sulphate. The chloroform was evaporated *in vacuo* to yield 730G. of a pale yellow oil.

d) Preparation of 2-(N-Benzyl-N-tertiary butylamino)-4'-hydroxy 3'-hydroxymethyl acetophenone hydrochloride

213G of 3 - (hydroxymethyl) - 4 - hydroxy - ω - bromacetophenone, 220g of benzyl-tertiary butylamine and 90 ml of benzene were stirred and heated at reflux for 18 hrs. After cooling the benzyl-tertiarybutylamine hydrobromide was removed by filtration and washed with benzene. The benzene solution was extracted with three 200ml portions of 2N. hydrochloric acid solution. The aqueous acid solution was then extracted with 500ml of ether, concentrated hydrochloric acid (65 ml) was added and the solution allowed to stand for 18 hrs. The precipitate was removed by filtration and washed with water. Crystallisation from water gave 90g. of the product as a white solid m.p. 174°C.

e) Preparation of α'-tertiary Butylaminomethyl-4-hydroxy-m-xylene-α',α'diol

120G of 2 - (N - Benzyl - N – tertiary butylamino) - 4' - hydroxy - 3' - hydroxymethyl acetophenone hydrochloride was shaken with 500 ml of 10% sodium carbonate solution and 500ml of ethyl acetate. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated. The residual gum was dissolved in 500ml of ethanol and hydrogenated with 10g of 10% palladium oxide on charcoal catalyst at 60°C and at atmospheric pressure. Two moles of hydrogen were absorbed in 3½ hrs. The catalyst was removed by filtration and the ethanol distilled *in vacuo*. The residual gum was refluxed with 500 ml of ethyl acetate for a few minutes and then allowed to cool. The white solid was removed by filtration and recrystallised from ethanol/ethyl acetate to yield 30G of the diol m.p. 151°C.

EXAMPLE 17

Preparation of 4-hydroxy-α'-[(methylamino)methyl]-m-xylene-α',α'-diol

a) α'-[(Benzylmethylamino)methyl]-4-hydroxy-m-xylene-α',α'-diol

21.3G of 5 - (N - benzyl - N - methylglycyl) - salicylic acid ethyl ester was dissolved in 140ml of tetrahydrofuran. This solution was added dropwise to a stirred suspension of 5.6g of lithium aluminium hydride in 175ml of dry tetrahydrofuran in an atmosphere of nitrogen. After the addition was completed, the mixture was stirred at room temperature for one hour, then 45ml of water was added dropwise. The tetrahydrofuran was removed by distilling *in vacuo* and dilute hydrochloric acid was added. The acid solution was basified with sodium bicarbonate solution and extracted with ether (5 × 50ml). The ethereal solution was washed three times with saline and after drying over anhydrous Na_2SO_4 it was evaporated *in vacuo* to give 8.7g of the product as a white solid, m.p. 132—134°C.

b) 4-Hydroxy-α^1-[(methylamino)methyl]-m-xylene-α^1,α^3-diol

2.0G of α^1 - [(benzylmethylamino)methyl] - 4 - hydroxy - m - xylene α^1,α^3 - diol were reduced in 30ml of ethanol containing 1ml of triethylamine and 1ml of water, using 0.5g of 10% palladium oxide on charcoal as catalyst. Hydrogen uptake was complete after 15 minutes. The catalyst was removed by filtration and the solution was evaporated to dryness *in vacuo* to give 1.55g of a friable solid. This base in methanol was added to a solution of 0.9g of maleic acid in methanol. The solution was warmed and ethyl acetate was added to effect crystallisation. 1.15G of the maleate were obtained as colourless needles, m.p. 109—111°.

EXAMPLE 18

Preparation of 3-hydroxy-α^2-(isopropylamino)methyl-p-xylene-α^1,α^4-diol

a) α^2-[Benzylisopropylamino]methyl-3-hydroxy-p-xylene-α^1,α^4-diol

A solution of 1.58g of N-benzylisopropylamine in 4ml of dry tetrahydrofuran was added all at once at approx. 10°, to a solution of 1.45g of 4-bromoacetylsalicylic acid, methyl ester in 4ml of dry tetrahydrofuran and the flask was stoppered and left to stand for 3 hours. The crystalline benzylisopropylamine hydrobromide which formed was filtered off and the filtrate was slowly added to a slurry of 1.7g of lithium aluminium hydride in 100ml of dry tetrahydrofuran, with stirring. The resulting mixture was heated to boiling and stirred under reflux for 15 minutes. After cooling and leaving to stand overnight, the excess lithium aluminium hydride was decomposed with the minimum of water and the resulting mixture was evaporated to dryness. The residue was shaken with dilute HCl and filtered. The filtrate was extracted with ether, then the aqueous layer was basified to pH 8 with sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated to dryness. The residue was allowed to crystallise from ether, giving 0.99g of yellowish crystals, m.p. 103—8°.

b) 3-Hydroxy-α^2-(isopropylamino)methyl-p-xylene-α^1,α^4-diol

0.6G of α^1 - [benzylisopropylamino]methyl - 3 - hydroxy - p - xylene - α^1,α^4 - diol was dissolved in 30ml of ethanol and to this solution was added 0.15g of triethylamine. This solution was hydrogenated over 0.15g of pre-reduced 10% palladium on carbon catalyst. A total of 46.5ml of hydrogen was absorbed in 10 minutes. After filtering and evaporating to dryness, the residue was crystallised from ethyl acetate/ether, then from tetrahydrofuran/petrol (b.p. 40—60°) and was then dried *in vacuo* at 50° for 3 hours to give 0.3g of a white crystalline solid, m.p. 103—5°C.

EXAMPLE 19

Preparation of 4-hydroxy-α^2-(1-isopropylaminopropyl)-m-xylene-α^1,α^3-diol

a) 5-(2-Bromo-butyryl)-salicylic acid, methyl ester

A solution of 104g of bromine in 1000ml of chloroform was added dropwise to a stirred solution of 144g of 5 - butyryl - salicylic acid, methyl ester in 300ml of chloroform at room temperature. The reaction was at first extremely slow, and only after about 1 hr. was hydrogen bromide gas evolved at an appreciable rate.

The bulk of the bromine solution was then run in over a further hour. The solution was stirred for an additional 15 mins cooled and washed three times with cold water. The solvent was distilled off under reduced pressure leaving a pure white solid residue which was recrystallised once from ethanol, to give 200g of the product, m.p. 83°.

b) 5-(2-Isopropylamino-butyryl)-salicylic acid, methyl ester hydrochloride

A solution of 45g of 5 - (2 - bromo - butyryl) - salicylic acid methyl ester and 30g of isopropylamine in 30 ml of methanol was boiled under reflux for 5 hrs. The mixture was evaporated under reduced pressure, the oily residue treated with dry ether, and the insoluble hydrobromide filtered off. The ethereal solution was boiled with charcoal and filtered. Dry hydrogen chloride gas was then bubbled into the solution and the hydrochloride precipitated as a white crystalline solid which was crystallised twice from methanol/ether, to give 20g, of the product, m.p. 250°C.

c) 4-Hydroxy-α^2-(1-isopropylaminopropyl)-m-xylene-α^1,α^3-diol

An aqueous suspension of 10g of 5 - (2 - isopropylaminobutyryl) - salicylic acid, methyl ester hydrochloride was basified with 10% sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$, the solvent evapora-

ted and the gummy residue, in 60ml of sodium-dried tetrahydrofuran, was added cautiously with stirring to 3.0g of lithium aluminium hydride in 300ml of dry tetrahydrofuran. The mixture was heated under reflux with stirring for 30 mins. and was then cooled. 21Ml of water was added dropwise with vigorous stirring and the mixture was allowed to stand overnight before the solvents were evaporated off. The solid residue was acidified with dilute hydrochloric acid to pH 6 and this solution was basified with dilute sodium hydroxide and sodium bicarbonate to pH 8. The gelatinous insoluble hydroxides were then centrifuged and the filtrate was continuously extracted with chloroform. The solvent was evaporated off and the oily basic residue taken up in ether. Dry hydrogen chloride gas was passed into the solution and the white crystalline precipitate thus obtained was filtered off and crystallised from ethanol, to give 5g of the product, m.p. 199°.

EXAMPLE 20

Preparation of 5-(2-amino-1-hydroxyethyl)-salicylic acid methyl ester hydrochloride

a) 5-(N,N-Dibenzylaminoglycyl)-o-anisic acid methyl ester hydrochloride

6.0G of 5 - bromoacetyl - o - anisic acid methyl ester (see Example 34(a)) and 7.8g of dibenzylamine in 200ml of ethyl methyl ketone were refluxed for 2 hours with stirring. Solid appeared within 2 mins. After removal of the dibenzylamine hydrobromide by filtration, the solution was evaporated to dryness and treated with ether. Some insoluble brown material was removed and hydrogen chloride was passed through the ethereal solution. The dark gummy solid which precipitated was recrystallised from methanol/ethyl acetate to give 2.0g of the hydrochloride as a white solid, m.p. 163—165°.

After two recrystallisations from methanol/ethyl acetate, colourless needles were obtained, m.p. 166—8°.

b) 5-(N,N-Dibenzylglycyl)-salicylic acid hydrobromide

2.0G of 5 - (N,N - dibenzylglycyl) - o - anisic acid, methyl ester hydrochloride and 40ml of 48% aqueous hydrobromic acid were refluxed for 2 hours. The initially clear solution gradually deposited a white solid. After being cooled the mixture was filtered to give 2.0g of the acid hydrobromide as a white solid, m.p. 165—166°.

c) 5-(N,N-Dibenzylglycyl)-salicylic acid methyl ester hydrochloride

8.78G of the acid hydrobromide obtained in-b) were refluxed with a mixture of 22% methanolic hydrogen chloride (20ml) and methanol (50ml) for 16 hrs. The solution was evaporated to dryness and an ethereal solution of the residue was shaken with sodium bicarbonate solution. The ethereal solution was dried over $MgSO_4$ and treated with methanolic hydrogen chloride to give 7.0g of a white solid, m.p. 167—169°.

d) 5-(2-Amino-1-hydroxyethyl)salicylic acid methyl ester hydrochloride

6.4G of 5 - (N,N - dibenzylaminoglycyl) - salicylic acid methyl ester hydrochloride in 150ml of methanol were hydrogenated in the presence of 1.0g of a 10% palladium oxide on charcoal catalyst. Uptake of hydrogen ceased after 9 hrs. The catalyst was removed by filtration, and the filtrate was concentrated and treated with ether to precipitate 2.75g of the product as a white solid, m.p. 168—170°, which was recrystallised from methanol/ethyl acetate to give colourless plates, m.p. 187—188°.

EXAMPLE 21

Preparation of α^1-aminomethyl-4-hydroxy-m-xylene-α^2,α^3-diol

A solution of 1.9g of α^1 - dibenzylaminomethyl - 4 - hydroxy - m - xylene - α^2,α^3 - diol in 50ml of ethanol and 5ml of water was shaken in an atmosphere of hydrogen in presence of 0.5g of pre-reduced 10% palladium on charcoal catalyst. Uptake of hydrogen was complete in 6 Hours. The catalyst was removed and the solution was evaporated to dryness under reduced pressure to leave 0.9g of the product as a cream solid, m.p. 151—152°.

EXAMPLE 22

Preparation of 5-[1-hydroxy-2(methylamino)ethyl] salicylic acid ethyl ester, hydrochloride

a) 5-(N-Benzyl-N-methylglycyl)-salicylic acid ethyl ester hydrochloride

20G of 5 - bromoacetylsalicylic acid ethyl ester, 15.2g of N - benzylmethylamine and 250ml of ethyl methyl ketone were stirred and refluxed for 1.5 hours. The solid that precipitated was filtered and the filtrate was evaporated *in vacuo* leaving a yellow oil.

Dry ether was added to the residue and the ethereal solution was filtered. The clear filtrate was treated with dry HCl gas and 13.4g of the white precipitate m.p. 158—160° was removed by filtration. Recrystallisation from ethanol/ether gave the product as colourless needles m.p. 169—171°C.

b) 5-[1-Hydroxy-2(methylamino)ethyl]-salicylic acid ethyl ester hydrochloride

3.0G of 5 - (N - benzyl - N - methylglycyl) - salicylic acid ethyl ester hydrochloride in 30ml of ethanol was hydrogenated with 1g of 10% palladium oxide on charcoal as catalyst. Hydrogen uptake was complete after 2.75 hours. The solution, after removal of the catalyst by filtration, was evaporated to dryness under reduced pressure, and the residue was crystallised from ethanol/ethyl acetate to give 1.6g of the product as colourless microneedles, m.p. 129—130°C.

EXAMPLE 23

Preparation of 5-[1-hydroxy-2-(p-methoxy-α-methylphenethyl) amino ethyl] salicylic acid, methyl ester, hydrochloride

1.08G of 5[(1 - hydroxy - 2 - amino)ethyl] salicylic acid methyl ester hydrochloride in 100ml of methanol, basified by the addition of 25ml of methanolic sodium methoxide containing 0.10g of sodium and 0.72g of p - methoxyphenyl - 2 - propanone, were hydrogenated in the presence of 1.0g of prereduced 10% palladium oxide on charcoal catalyst, suspended in 25 ml of methanol. Uptake of hydrogen ceased within twenty hours. The solution was filtered and evaporated, and the resulting oil was dissolved in ether. After filtering to remove sodium chloride, ethereal hydrogen chloride was added to the ether solution to precipitate an oil which gradually solidified within 15 minutes. The solid crystallised from acetone/ether to give 0.6g of the product as white crystals m.p. 155—161°.

EXAMPLE 24

Preparation of 4-hydroxy-α^1-{[(2-indol-3-yl-1-methylethyl) amino]methyl}-m-xylene-α^1,α^3-diol hydrogen tartrate

a) 5-{1-Hydroxy-2-[(2-indol-3-yl-1-methylethyl)amino]ethyl}-salicylic acid methyl ester

A solution of 0.71g of sodium hydroxide in ethanol was added to a solution of 4.4g of 5 - (2 - amino - 1 -hydroxyethyl) - salicylic acid methyl ester hydrochloride in ethanol. The total volume of the solution was 250ml. Sodium chloride was then removed and the solution was hydrogenated in presence of 1.0g of 10% palladium on charcoal catalyst and 3.8g of indol - 3 - yl - 2 - propanone. Uptake of hydrogen ceased after 25 hours. The catalyst and solvent were removed to leave a straw coloured oil. This was separated from sodium chloride by solution in ether, followed by filtration and evaporation to give 7.1g of the crude ester as an oil.

b) 4-Hydroxy-α^1-{[2-indol-3-yl-1-methylethyl)amino]methyl}-m-xylene-α^1,α^3-diol, hydrogen tartrate

6.5G of 5 - {1 - hydroxy - 2[(2 - indol - 3 - yl - 1 - methylethyl)amino]ethyl} salicylic acid methyl ester in 100ml of tetrahydrofuran were added to a stirred suspension of 1.4g of lithium aluminium hydride in 50ml of tetrahydrofuran, in an atmosphere of nitrogen, at a rate sufficient to maintain refluxing of the solvent. After 1 hour, 10ml of water was cautiously added and the mixture was concentrated under reduced pressure. The residue was treated with dilute hydrochloric acid and non-basic indole derivatives were removed by extraction with ethyl acetate.

The acid solution was neutralised with sodium bicarbonate and extracted four times with ethyl acetate. After being dried over $MgSO_4$ and evaporated, the latter yielded 2.0g of a buff friable solid. This base was dissolved in 30ml of ethyl acetate

and added to a solution of 0.8g of racemic tartaric acid in 30ml of methanol, to precipitate a pale brown gum. When triturated with ethyl acetate this slowly yielded 1.6g of a friable tan solid m.p. *ca* 93—100°. Recrystallisation from methanol/dry ether afforded a brown gum which when triturated with dry ether gave 0.8g of the product as a buff solid m.p. ca. 112°, frothing from ca 70°.

EXAMPLE 25

Preparation of 5-{1-hydroxy-2-[(1-methyl-2-piperidinoethyl) amino]ethyl} salicylic acid methyl ester

3.65G of 5 - [(2 - amino - 1 - hydroxy)ethyl]salicylic acid methyl ester hydrochloride in 75ml of methanol were basified by the addition of 25 ml of methanolic sodium methoxide containing 0.34g of sodium, and then added to 2.10g of 1 - piperidino - 2 - propanone. The mixture was hydrogenated in the presence of 1g of 10% palladium oxide on charcoal catalyst suspended in 25ml of methanol. Uptake of hydrogen was complete within 25 hours.

The solution was filtered and evaporated and the resulting oil was separated from sodium chloride by extraction with ethyl acetate. The ethyl acetate was evaporated and the resulting oil taken up in acetone/ether. The solution deposited an oil which after two days formed a solid. This was recrystallised from cyclohexane/light petroleum (b.p. 60—80°), to yield white crystals of the product, m.p. 112.5—113.5°.

EXAMPLE 26

Preparation of 4-hydroxy-α^1-{[(1-methyl-2-phenoxyethyl)amino] methyl}-m-xylene-α^1,α^3-diol

a) 5-{1-Hydroxy-2-[(1-methyl-2-phenoxyethyl)amino]ethyl}- salicylic acid methyl ester

5.0G of 5 - (N,N - dibenzylglycyl) - salicylic acid methyl ester hydrochloride in ethanol was reduced with hydrogen in presence of 1.0g pre-reduced 10% palladium on charcoal catalyst. After 17 hours uptake of hydrogen ceased.

A solution of 0.45g of sodium hydroxide in 20ml of ethanol and 1.9g of 1 - phenoxy - 2 - propanone was added and reduction was continued in presence of a similar quantity of fresh catalyst. After 52 hours uptake of hydrogen ceased. The catalyst and solvent were removed and the residue was partitioned between water and ether. The ether was dried and removed to leave 3.0g of the crude ester as a pale amber oil.

b) 4-Hydroxy-α^1-{[(1-methyl-2-phenoxyethyl)amino]methyl}- m-xylene-α^1,α^3-diol

2.7G of 5 - {1 - Hydroxy - 2 - [(1 - methyl - 2 - phenoxyethyl)amino]ethyl} - salicylic acid methyl ester dissolved in 50ml of dry tetrahydrofuran, were added to a warm stirred suspension of 0.6g of lithium aluminium hydride in 20ml of tetrahydrofuran, in an atmosphere of nitrogen, at a rate to maintain the solvent at the reflux. The resulting white gelatinous precipitate was stirred and warmed for 1 hour, then cooled and decomposed by dropwise addition of 5ml of water. The mixture was concentrated under reduced pressure, more water was added and the pH was adjusted to 8 by addition of hydrochloride acid followed by sodium bicarbonate.

The mixture was extracted with ethyl acetate, which was dried and evaporated to yield an amber oil. Trituration with ether gave 0.9g of the triol as a cream solid. Recrystallisation from ethyl acetate/cyclohexane afforded a white solid m.p. 128—130°C.

EXAMPLE 27

Preparation of 4-hydroxy-α^1-[(α-methylphenethylamino)methyl]- m-xylene-α^1,α^3-diol.

a) 5-[1-Hydroxy-2-(α-methylphenethylamino)ethyl]-salicylic acid methyl ester

3.2G of 5 - (N,N - dibenzylaminoglycyl) - salicylic acid methyl ester and 1.2g of benzyl methyl ketone in 100ml of ethanol were shaken in an atmosphere of hydrogen in presence of 1.0g of 10% prehydrogenated palladium on charcoal catalyst. Uptake of hydrogen ceased after 40 hours. The catalyst and solvent were removed to give an oil which was extracted into dilute hydrochloric acid and ether. The aqueous solution was washed with ether and treated with excess sodium bicarbonate solution. The liberated base was extracted by ether which was washed, dried over $MgSO_4$ and evaporated to give 1.3g of the crude basic ester as a colourless oil.

b) 4-Hydroxy-α^1-[(α-methylphenethylamino)methyl]-m-xylene-α^1,α^3-diol

1.3G of 5 - [1 - hydroxy - 2 - (α - methylphenethylamino)ethyl] - salicylic acid methyl ester in 20ml of dry tetrahydrofuran were added to a stirred suspension of 1.5g of lithium aluminium hydride in 50ml of dry tetrahydrofuran at a rate to maintain refluxing of the solvent.

After 1 hour at the reflux the mixture was cooled and decomposed by dropwise addition of 5ml of water, with stirring. The mixture was evaporated nearly to dryness under reduced pressure and the residue was treated with excess dilute hydrochloric acid, followed by sodium bicarbonate solution.

The resulting basic mixture was extracted four times with ethyl acetate which was dried and evaporated to yield a yellow oil. When triturated with ether this gave 0.3g of the product as a white solid. Recrystallisation from ethyl acetate gave colourless crystals, m.p. 113—115°.

The *p* - hydroxy - α - methyl compound has been prepared by processes analogous to those described above for the unsubstituted α-methyl compound. The structure of p - hydroxy - α - methyl compound, that is, 4 - hydroxy - α^1 - [(p - hydroxy - α - methylphenethylamino)methyl] - m - xylene - α^1,α^3 - diol was confirmed by nuclear magnetic resonance and ultraviolet and infra red spectra.

EXAMPLE 28

Preparation of 4-hydroxy-α^1-{[(3,4,5-trimethoxy-α-methylphenethyl)-amino]methyl}-m-xylene-α^1,α^3-diol

4-Hydroxy-α^1-{[(3,4,5-trimethoxy-α-methylphenethyl)amino]methyl}-m-xylene-α^1,α^3-diol

1.7G of α^1 - aminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol in 12.5ml of methanol containing 1g of triethylamine, and 2.2g of (3,4,5 - trimethoxyphenyl) - 2 - propanone were hydrogenated in the presence of 0.25g of pre-reduced Adams catalyst suspended in 15ml of water. Uptake of hydrogen ceased within 16 hours.

The solution was filtered and evaporated, and the resulting oil extracted with boiling benzene. On cooling the solution, a white gum was deposited which, on standing overnight in a small volume of ether followed by drying *in vacuo* at 40° for 24 hours, gave 1.65g of the product as white crystals, m.p. 90—98°.

EXAMPLE 29

Preparation of 4-hydroxy-α^1-{[(p-methoxy-α-methylphenethyl)-amino]methyl}-m-xylene-α^1,α^3-diol

1.03G of α^1 - aminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol in 75ml of methanol containing 10ml of water, 0.5 g of triethylamine and 0.92g of p - methoxyphenyl - 2 - propanone were hydrogenated in the presence of 0.5g of pre-reduced Adams catalyst suspended in 25ml of methanol.

Uptake of hydrogen ceased within fifteen hours. The solution was then filtered and evaporated, and the resulting oil was extracted with boiling benzene. On cooling the solution, a white gum was deposited, which, on drying *in vacuo* over paraffin wax, gave 0.70g of the product as white crystals, m.p. 81—83°C.

EXAMPLE 30

Preparation of 4-hydroxy-α^1-{[(1-methyl-2-morpholinoethyl)-amino]methyl}-m-xylene-α^1,α^3-diol

1.63G of -α^1 - aminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol in 110ml of methanol, containing 1.0g of triethylamine, and 1.22g of 1 - morpholino - 2 - propanone, were hydrogenated in the presence of 0.25g of pre-reduced Adams catalyst suspended in 15ml of water. Uptake of hydrogen ceased within 16 hr.

The solution was filtered and evaporated to give an oil which only partially solidified. Crystallisation from ethyl acetate gave an oil, which when triturated, afforded the product as a white solid. 0.60G. of the product, m.p. 134—145° was obtained.

EXAMPLE 31

Preparation of 4-hydroxy-α^1-[(4-hydroxy-1-methylbutyl) amino]methyl-m-xylene-α^2,α^3-diol

1.5G of α^1 - aminomethyl - 4 - hydroxy - m - xylene - α^2,α^3 - diol in 85 ml of methanol containing 15ml of water, 0.5g of triethylamine and 0.87g of 5 - hydroxy - 2 - pentanone were hydrogenated in the presence of 0.16g of pre-reduced Adams catalyst suspended in 25 ml. of methanol.

After 60 hours, uptake of hydrogen ceased, but thin layer chromatography showed that some of the unchanged primary amine was still present. Reduction was continued in the presence of a further portion of 0.16g of pre-reduced Adams catalyst. Uptake ceased after a further 25 hours when thin layer chromatography showed only a trace of the primary amine.

The solution was filtered and evaporated to give an oil which, on trituration with dry ether and prolonged drying *in vacuo*, became a white, highly deliquescent, friable solid. A preparative thin layer chromatogram (silica/methanol) containing 3% 0.880 ammonia solution on 280mg of this solid gave two fractions at Rf 0.60 and Rf 0.80, visible under U.V. light. The former was extracted with dry methanol (2 × 50 ml) to give 140mg of a white, highly deliquescent friable solid. The N.M.R. spectrum showed the structure of this solid to be consistent with the required base, although it contained *ca.* 10% of the product of hydrogenolysis of the α^3 alcohol group.

EXAMPLE 32

Preparation of 4-hydroxy-α^1-{[(α-methyl-p-ethoxyphenoxyethyl amino]methyl}-m-xylene-α^2,α^3-diol

1.5G of α^1 - aminomethyl - 4 - hydroxy - m - xylene - α^2,α^3 - diol in 110ml of methanol containing 1g of triethylamine and 1.63g of (p-ethoxyphenoxy)-2-propanone were hydrogenated in the presence of 0.20g. of pre-reduced Adams catalyst. Uptake of hydrogen ceased within 17 hr.

The solution was filtered and evaporated to give an oil which was extracted with ether (2 × 50ml). The ether was evaporated to give a gum which was crystallised from ethyl acetate/cyclohexane to yield a gum which solidified after drying *in vacuo* for 3 days. Recrystallisation from ethyl acetate/cyclohexane gave 0.30g. of the product as white prisms, m.p. 98—107°.

EXAMPLE 33

Preparation of α^1-(cyclopentylaminomethyl)-4-hydroxy-m-xylene-α^2,α^3-diol

a) 5-(N,N-Dibenzylglycyl)-salicylic acid acid methyl ester hydrochloride

24.1G of dibenzylamine were added to a solution of 18.5g of 5 - (bromoacetyl)-salicylic acid methyl ester in 500ml of ethyl methyl ketone. After being refluxed with stirring for 3 hours the precipitated dibenzylamine hydrobromide was removed. The solution was evaporated to dryness and treated with ether. 2.8G of an insoluble solid were removed by filtration and HCl gas was passed through the filtrate to precipitate 22.1g of the product. When recrystallised from methanol/ethyl acetate 18.0g. of a white solid m.p. 174—176° were obtained.

b) α^1-Dibenzylaminomethyl-4-hydroxy-m-xylene-α^2,α^3-diol

10G of 5 - (N,N - dibenzylglycyl) - salicylic acid methyl ester hydrochloride were basified with sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The basic residue in 100ml of dry tetrahydrofuran was added to a suspension of 1.74g. of lithium aluminium hydride in 500ml of dry tetrahydrofuran. A white gelatinous precipitate formed which partially dissolved on heating. The stirred mixture was refluxed for 6 hours, then cooled and 5 ml of water was added dropwise with stirring. The cloudy mixture was evaporated under reduced pressure and the residue was treated with 100ml of 5N hydrochloric acid. The oily hydrochloride which precipitated was separated from the acid solution, washed with a little water and treated with sodium bicarbonate solution. The liberated base was extracted into ether which was dried and evaporated to yield 6.8g. of the product as a white solid, m.p. 105—107°. Recrystallisation from ether/light petroleum (b.p. 40—60°) gave 5.7g. of colourless rods, m.p. 110—111°.

c) α^1-(Cyclopentylaminomethyl)-4-hydroxy-m-xylene-α^1,α^3-diol

3.0G of α^1 - (dibenzylaminomethyl) - 4 - hydroxy - m - xylene - α^1,α^3 - diol dissolved in 100ml of ethanol and 5ml of water were reduced in the presence of 1.0g of triethylamine and 1.0g of 10% pre-reduced palladium on charcoal catalyst.

Hydrogen uptake ceased after 2.5 hours and 0.76g of cyclopentanone was then added and reduction was continued. Owing to slow uptake of hydrogen the catalyst was replaced by 0.5g of prehydrogenated Adam's platinum oxide and reduction was completed within 1 hour. After removal of catalyst the solution was evaporated to dryness and the resultant oil was triturated with ether to give 0.9g of the cyclopentylamino triol as a white solid, m.p. 121—124°, which was crystallised from ethyl acetate to give a white solid, m.p. 129—131°.

EXAMPLE 34

Preparation of 5-(1-hydroxy-2-isopropylaminoethyl)-salicylic acid hydrobromide

a) 5-Bromoacetyl-o-anisic acid methyl ester

1.4G of bromine in 10ml of chloroform were added dropwise to a stirred solution of 1.7g of 5 - acetyl - o - anisic acid methyl ester in 50ml of chloroform at 0—10°, at a rate which just maintained decolourisation of the bromine. The solution was evaporated under reduced pressure to leave 1.93g of the crude bromoacetyl ester as a white solid, m.p. 143—144°. Recrystallisation from methanol gave colourless plates, m.p. 153—154°C.

b) 5-(N-Benzyl-N-isopropylglycyl)-o-anisic acid methyl ester hydrochloride

A solution of 10g of 5 - bromoacetyl - o - anisic acid methyl ester and 11.0g of benzylisopropylamine in 200ml of ethyl methyl ketone was stirred and refluxed for 6.5 hours. The precipitated benzylisopropylamine hydrobromide was filtered off and the filtrate was evaporated to dryness. The residue was triturated with 250ml of ether and separated from a little insoluble material, and the ethereal solution was treated with gaseous hydrogen chloride. A brown gum was obtained which crystallised from a mixture of methanol and ethyl acetate to give 6.14g of the product as colourless plates, m.p. 194—195°.

c) 5-(N-Benzyl-N-isopropylglycyl)salicylic acid hydrobromide monohydrate

3.3G of 5 - (N - benzyl - N - isopropylglycyl) - o - anisic acid methyl ester hydrochloride and 50ml of 48% hydrobromic acid were refluxed together for 5 hours. The solution was cooled and filtered to give 2.8g of the acid hydrobromide as a white solid m.p. 186.5—188°. Recrystallisation from water and drying at 100°/12mm. gave colourless prisms, m.p. 188—90°C.

d) 5-(1-Hydroxy-2-isopropylaminoethyl)-salicylic acid hydrobromide

A solution of 2.9g of 5 - (N - benzyl - N - isopropylglycyl)salicylic acid hydrobromide in 50 ml of ethanol was reduced in an atmosphere of hydrogen in the presence of 0.5g of 10% palladium on charcoal catalyst. Hydrogen uptake was complete after 23 hours.

The solution after removal of catalyst, was evaporated under reduced pressure to give 2.61g of an amber syrup which, when triturated with ethyl acetate and ether, gave 1.93g of the product as a white solid m.p. 164—166°.

Recrystallisation from methanol/ethyl acetate gave colourless prisms m.p. 165—166° after being dried at 100°/12mm.

EXAMPLE 35

Preparation of β-[5-(2-tert-butylamino-1-hydroxy)ethyl-2-hydroxy]phenyl-ethanol

a) 3-(β-Acetoxyethyl)-4-hydroxyacetophenone

A solution of 15.0g of β - (p - hydroxyphenyl) - ethanol in 120ml of 40% w/w boron trifluoride-acetic acid complex was heated with stirring at 65° for 16 hours, during which time the colour became pale-brown. The solution was cooled and treated with hydrated sodium acetate, then with water, and the mixture was extracted three time with ether. The combined ethereal extracts were dried over anhydrous sodium sulphate and evaporated to give 23g of the product as a brown oil.

b) 4-Acetoxy-3-(β-acetoxyethyl)acetophenone

A mixture of 23.0g of 3 - (β - acetoxyethyl) - 4 - hydroxyacetophenone, 8.2g of acetyl chloride, 46g of anhydrous potassium carbonate and 500 ml of ethyl methyl ketone was refluxed with stirring for 4 hours. The solids were then filtered off and the solvent was evaporated to give an orange oil, which was chromatographed, using 600g of silica gel. Eluting with 20% ethyl acetate in benzene gave 15g of the required product as a mobile straw-coloured oil.

c) 4-Acetoxy-3-(β-acetoxyethyl)phenacyl bromide

3.66G of bromine in 75ml of chloroform was added dropwise, over 70 minutes to a stirred solution of 6.0g of 4 - acetoxy - 3 - (β - acetoxyethyl) acetophenone in 75 ml of chloroform, at room temperature. Stirring was continued for a further 10 minutes then the solution was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 7.3g of 4 - acetoxy - 3 - (β - acetoxyethyl)phenacyl bromide as a brown oil.

d) β-[5-(2-benzyl-tert-butylamino-1-hydroxy)ethyl-2-hydroxy] phenyl ethanol

4.3G of 4 - acetoxy - 3 - (β - acetoxyethyl)phenacyl bromide and 4.1g of benzyl *tert* butylamine were dissolved in 20ml of dry tetrahydrofuran and the solution was left to stand at room temperature for 7 days. Benzyl *tert*-butylamine hydrobromide was formed and was filtered off. The filtrate was added dropwise over 40 minutes to a stirred suspension of 1.5g of lithium aluminium hydride in 30ml of tetrahydrofuran. The tetrahydrofuran refluxed gently as the solution was added and a gelatinous solid precipitated.

Stirring was continued for 2 hours at 70°, then the mixture was cooled to 0° and 15ml of water was added cautiously to the cold stirred mixture. The mixture was stirred for 1 hour, then dilute hydrochloric acid was added until the mixture was slightly acidic. The pH was adjusted to about 8 by the addition of sodium carbonate solution. The mixture was filtered, and the filtrate was extracted four times with chloroform. The combined chloroform extracts were washed once with water and dried over anhydrous sodium sulphate and the chloroform was evaporated to give 1.8g of brown oil.

The oil was refluxed with 500ml of light petroleum (b.p. 60—80°) for 10 minutes and the solution was decanted and left to stand at room temperature over-night to give a white solid which was filtered as a first crop.

On treatment with benzene some of the remaining oil dissolved. The solution was decanted, treated with charcoal and evaporated to give 0.8g of a pale-brown oil. This was dissolved in ethanol and addition of water gave a whitish solid. Further recrystallisation from aqueous ethanol gave a second crop of product as a pure-white solid. The total yield of the product was 265mg., m.p. 133—134.5°C.

e) β-[5-(2-tert-Butylamino-1-hydroxy)ethyl-2-hydroxy] phenylethanol

211Mg of β - [5 - (2 - benzyl - tert - butylamino - 1 - hydroxy - ethyl - 2 - hydroxy]phenylethanol was hydrogenolysed at room temperature in 30 ml of ethanol over 10% palladium catalyst on charcoal. Hydrogen uptake ceased in 30 minutes. The catalyst was filtered off and the filtrate was evaporated to give a greenish-yellow oil, which solidified after deep freezing. The solid, however could not be recrystallised. 144Mg. of the product, m.p. 54—60°, was obtained.

EXAMPLE 36

Preparation of α^1-tert-butylaminomethyl-α^3-diphenyl-4-hydroxy-xylene-$\alpha^1\alpha^3$-diol hydrochloride

A solution of phenyl magnesium bromide in ether (45%, 50mL; slight excess of ca 5 mole equivalents) was added in a thin stream to a stirred solution of 5 - (2 - tert. butylamino - 1 - hydroxyethyl)salicylic acid methyl ester (5.0g) in dry tetrahydrofuran (200 ml.). The mixture was refluxed overnight (15 hours), cooled and poured onto ice cold saturated ammonium chloride solution. The organic layer was separated, washed with saturated ammonium chloride solution, dried over sodium sulphate, and evaporated. As thin layer chromatography (silica-cyclohexane-ethyl acetate, 3 : 1) indicated the presence of a non-basic impurity, the crude oil was dissolved in ethyl acetate (25 ml.) and treated with a slight excess of ethereal hydrogen chloride with cooling. The precipitate was filtered off and dried to give α^1 - tert - butylaminomethyl - α^3 - diphenyl -

4 - hydroxy - m - xylene - $\alpha^1\alpha^3$ - diol, hydrochloride, 6.3g. (78.3%) m.p. 180—190°, with decomposition.

This material was dissolved in a small amount of tetrahydrofuran, filtered and ethyl acetate (20 ml.) added and allowed to crystallise to afford 4.8g. m.p. 186—7° with decomposition.

EXAMPLE 37

Preparation of α^1-[(benzyl tert-butylamino)methyl]-4-hydroxy-α^3-methyl-m-xylene $\alpha^1\alpha^3$-diol

a) 4-Acetoxy-3-Bromoacetophenone

A solution of 3 - bromo - 4 - hydroxyacetophenone (25g.) in acetic anhydride (125ml) was refluxed for one hour. The excess acetic anhydride was then evaporated, in vacuo to give a brown oil (29.2g).

The product was distilled at reduced pressure.

Yield = 25.5g.

B.pt. = 128—130° at 0.05 mms.

b) 4'-Acetoxy-2,3'-dibromoacetophenone

40 drops of a solution containing bromine (15.8g) in chloroform (500 ml.) was added to a stirred solution of 4 - acetoxy - 3 - bromoacetophenone (25.4g) in chloroform (800ml), which contained 4 drops of hydrobromic acid in acetic acid. A golden-yellow colour was produced and the stirred solution was warmed (40°) for a few minutes. The colour quickly disappeared and the temperature of the stirred solution was maintained at 20—23° while the rest of the bromine solution was added dropwise over 2½ hours.

The solution was washed with water (×4), dried over magnesium sulphate and evaporated to give a greenish-yellow oil which suddenly crystallised to a cream-coloured solid.

Recrystallisation from ethanol gave the product as a white solid.

Yield = 24g.

m.p. = 73—78°

c) 4'-Acetoxy-3'-bromo-2-benzyltert butylamino acetophenone

A solution of 4' - Acetoxy - 2,3' - dibromoacetophenone (8.5g) and benzyl, tert-butylamine (8.3g) in dry methyl ethyl ketone (120ml) was refluxed for 2½ hours. Crystals of benzyl,tert.butylamine hydrobromide were deposited and these were filtered after the mixture had been cooled. Evaporation gave an orange oil which was treated with ether to precipitate more hydrobromide. This was filtered and the ether solution was evaporated to give the product as an orange oil which was used directly, without further purification.

Yield = 11.5g.

d) α-[(Benzyltertbutylamino)methyl]-3-bromo-α-hydroxy-p-cresol

4' - Acetoxy - 3' - bromo - 2 - benzyltertbutylaminoacetophenone (11.5g.) in ethanol (50ml.) was added dropwise over 5 minutes to a suspension of sodium borohydride (6g.) in ethanol (70 ml). The temperature was kept at 30—40° and a vigorous effervescence occurred during the addition. The solution was left to stand at room temperature overnight, then water was added and the ethanol was evaporated. The product was extracted into ether (×10) at pH 12 and the combined ethereal extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to give an orange oil.

Treatment with hot aqueous ethanol (charcoal) then cooling gave a crystalline solid, which was recrystallised from aqueous ethanol three times, giving the required product as an off white solid.

Yield = 2.3g.

m.p. = 139—140.5

e) α^3-[(Benzyltertbutylamino)methyl]-4-hydroxy-α^3-methyl-m-xylene-$\alpha^1\alpha^3$-diol

(1.135g) of α - [(Benzyltertbutylamino)methyl] - 3 - bromo - α - hydroxy - p - cresol in dry T.H.F. (20ml) was added dropwise over 40 minutes under nitrogen to a stirred solution of n-butyllithium in ether (.9N, 13.8ml.). An orange, milky precipitate was produced and some heat was given out during the addition. The mixture was gently refluxed for 10 minutes, then left at room temperature for 1 hour.

Acetaldehyde (0.52g., 4 moles) in ether (15ml) was added dropwise, over 5 minutes to the stirred mixture, whereupon most of the solid was dissolved. The solution was further refluxed for 45 minutes then poured into water. Ammonium chloride was added

and the product was extracted with ether (three times). The combined ethereal extracts were washed with saturated brine solution, dried over anhydrous sodium sulphate and evaporated on a rotary evaporator, without using heat, to give a brown oil, yield 1.1g.

Chromatography of 150 mg of this crude product on silica gave 50 mg of an oil which failed to crystallise. An NMR of this material indicated that it contained some of the required diol. The doublet at τ8.6 due to the methyl of the side chain —CH(OH)CH_3 was readily identified.

EXAMPLE 38

Preparation of α^3-dimethyl-4-hydroxy-α^1-isopropylamino methyl-m-xylene-$\alpha^1\alpha^2$-diol

a) 4-Benzyloxy-α^1-(N-benzyl-N-isopropylamino)methyl-α^3-dimethyl-m-xylene-$\alpha^2\alpha^3$-diol

A solution of 1.5g of 2 - benzyloxy - 4 - [2 - N - benzyl,N - isopropylamino - 1 - hydroxyethyl]benzoic acid, methyl ester in 50ml of tetrahydrofuran (50 ml) was treated with an excess of methyl magnesium bromide in 50 ml of ether and stirred at room temperature overnight. The mixture was poured on to saturated ammonium chloride solution and the organic layer separated, filtered through cotton wool, and evaporated to dryness to yield a gum.

Trituration of a portion of this gum with dilute hydrochloric acid gave a water insoluble salt, which was recrystallised from tetrahydrofuran-ethyl acetate to give colourless crystals of 4 - benzyloxy - α^1 - (N - benzyl - N - isopropylamino)methyl - α^3 - dimethyl - m - xylene - $\alpha^1\alpha^2$ - diol, hydrochloride m.p. 174.5—175°.

b) α^3-Dimethyl-4-hydroxy-α^1-isopropylaminomethyl-m-xylene -$\alpha^1\alpha^2$-diol

A solution of 1.2g. of 4 - benzyloxy - α^1 - (N - benzyl - N - isopropylamino)-methyl - α^3 - dimethyl - m - xylene - $\alpha^2\alpha^3$ - diol in 10ml of methanol was added to 0.2g of pre-reduced 10% palladium on carbon in 10 ml of methanol and hydrogenated until uptake of hydrogen ceased. The catalyst was filtered off and the filtrate evaporated to leave 0.9g of a pale yellow gum.

The gum was dissolved in ether and treated with an ethereal solution of o-benzyl benzoic acid to afford 1.08g of a crystalline salt m.p. 161—162°.

Recrystallisation from tetrahydrofuran ether gave 0.8g of α^3 - dimethyl - 4 - hydroxy - α^1 - isopropylaminomethyl - m - xylene - $\alpha^1\alpha^2$ - diol, o - benzoyl - benzoate m.p. 162—4°.

EXAMPLE 39

Preparation of 5-{1-hydroxy-2-[(1-methyl-2-phenoxyethyl) amino]ethyl}salicylamide

a) 5-{1-Hydroxy-2-[(1-methyl-2-phenoxyethyl)amino]ethyl} salicylic acid methyl ester

5 - [(2 - Amino - 1 - hydroxy-ethyl]salicylic acid methyl ester hydrochloride (2.53g.) in methanol (60 ml.) was basified by the addition of methanolic sodium methoxide (25 ml. containing 0.24 g. of sodium; 1 mol.) and was added to 1 - phenoxy - 2 - propanone (1.53g.; 1 mol.; redistilled b.p. 74°/0.7mm.). The mixture was hydrogenated in the presence of prehydrogenated 10% PdO/C catalyst (1g.) suspended in methanol (25 ml.). Uptake of hydrogen was complete within 25 hours.

The solution was filtered and evaporated, and the resulting oil was separated from sodium chloride and a trace of unchanged primary amine by washing with water and extracting into ether (150 ml.). The ether was dried [$MgSO_4$] and evaporated to give the crude ester as an oil [2.7 g.].

b) 5-{1-Hydroxy-2-[(1-methyl-2-phenoxyethyl)amino]ethyl} salicylamide

The crude ester of (a) (2.70g.) was dissolved in methanol (20 ml.) and ammonia solution d. 0.880 (20 ml) and allowed to stand in a stoppered flask for five weeks.

The solution was evaporated and the residual oily solid in methanol (7 ml) was charomatographed on a column of silica (25 g.) in ethyl acetate.

Elution with ethyl acetate gave the following fractions

a)	50ml. TLC SiO_2/MeOH	2 spots Rf 0.7 and Rf 0.9
b)	650 ml.	1 spot Rf 0.7
c)		2 spots Rf 0.30 and 0.70

Fraction (b) was evaporated to give a friable solid (ca. 0.60g.) which crystallised from benzene to give white crystals of the amide. (260 mg.) m.p. 126.5—128.5°C.

EXAMPLE 40

Soluble tablets, suitable for sub-lingual administration, containing 1mg of active ingredient, present as the sulphate

Formula	1 mg Tablet	10,000 Tablets
α^1 t-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol sulphate	1.2 mg	120.0 g.
granular mannitol	87.0 mg	870.0 g.
magnesium stearate	0.9 mg	9.0 g.
stearic acid	0.9 mg	9.0 g.
	90.0 mg	900.0 g.

Method

The four ingredients are mixed together, and the mixed powder is compressed on a suitable tablet machine fitted with 1/4" normal concave punches, to produce tablets of the correct weight.

EXAMPLE 41

Tablets suitable for oral administration.

Formula	1 mg Tablet (as base)	10,000 Tablets
α^1-t-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol sulphate	1.2 mg	12.0 g.
calcium sulphate dihydrate	88.2 mg	882.0 g.
maize starch	24.0 mg	240.0 g.
Amijel*	6.0 mg	60.0 g.
magnesium stearate	0.6 mg	6.0 g.
	120.0 mg	1200.0 g.

* Amijel is a partly hydrolysed corn starch product forming a sol in cold water.

Method

1. All the ingredients except the magnesium stearate, are mixed together, the mixed powders are granulated with water, and the damp mass is passed through a 16 mesh screen.
2. The wet granules are dried, and then passed through a 20 mesh screen.
3. The dried granules and the magnesium stearate are mixed together and compressed on a suitable tablet machine fitted with 1/4" normal concave punches, to produce the required tablets.

EXAMPLE 42

An aerosol formulation, expressed in terms of a single metered dose.

Formula	100 μg dose
α^1-t-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol	100 μg
oleic acid	10 μg
dichlorodifluoromethane	61 mg
trichlorofluoromethane	24 mg

Method

The active ingredient, the oleic acid and part of the dichlorodifluoro-methane are mixed together. The suspension is then diluted with the remainder of the dichlorodifluoromethane, and the requisite quantity is filled into aluminium aerosol containers which are closed by a suitable metering valve. The containers are then pressurised with trichlorofluoromethane.

EXAMPLE 43

Formula	100 μg dose
α^1-t-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol sulphate	120 μg
Sorbitan Trioleate	120 μg
Dichlorodifluoromethane B.P.C.	61 mg.
Trichlorofluoromethane B.P.C.	24 mg.

Method

Mix together the active ingredient, sorbitan trioleate, and part of the dichlorodifluoromethane. The suspension is then diluted with the remainder of the dichlorodifluoromethane, and the requisite quantity is filled into aluminium aerosol containers, which are closed by a suitable metering valve. The containers are then pressurised with trichlorofluoromethane.

EXAMPLE 44

Formula	100 μg dose
α^1-t-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol sulphate	120 μg
2-Dimethylaminoethanol	26.6 μg
Oleic Acid B.P. 1963	93.4 μg
Dichlorodifluoromethane B.P.C.	61 mg
Trichlorofluoromethane B.P.C.	24 mg

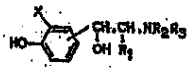
Method

The active ingredient, the oleic acid, the 2-dimethylaminoethanol and part of the dichlorodifluoromethane are mixed together. The suspension is then diluted with the remainder of the dichlorodifluoromethane, and the requisite quantity is filled into aluminium aerosol containers, which are closed by a suitable metering valve. The containers are then pressurised with trichlorofluoromethane.

In the above compositions, the amount of active ingredient may be varied widely and the sulphate may be replaced by any other salt having a pharmaceutically acceptable anion.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



and physiologically acceptable acid addition salts thereof, in which

R_1 represents a hydrogen atom or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms;

R_2 represents a hydrogen atom, or a benzyl group;

R_3 represents a hydrogen atom, or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms which radical may be substituted by hydroxyl groups, amino groups or heterocyclic rings containing 1 or more hetero atoms, for example morpholino, or represents a cycloalkyl, aralkyl or aryloxyalkyl radical which radicals may optionally be substituted for example by 1 or more alkoxy or hydroxy groups;

X represents a hydroxyalkyl or hydroxyaralkyl radical having a straight or branched alkyl chain containing from 1 to 6 carbon atoms, or a carboxy radical, or an alkoxy-carbonyl radical of the formula $—COOR_4$ (where R_4 represents a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms), or represents a radical of the formula —CONHOH or $—CONHNH_2$ or an amido radical of the formula $—CONR_5R_6$ (where R_5 and R_6, which may be the same or different, each represent a hydrogen atom or an arylalkyl radical or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms which may be substituted by hydroxyl or amino groups or where R_5 and R_6 together with the adjacent nitrogen atom form a heterocyclic ring which may contain additional hetero atoms).

2. Compounds as claimed in Claim 1 in which the side chain substituent is in the para position to the phenolic hydroxyl group or in the para position to the substituent X.

3. α^1-*tert.*-butylaminomethyl-4-hydroxy-*m*-xylene-α^1,α^2-diol.

4. 4-hydroxy-α^1-isopropylaminomethyl-*m*-xylene-α^1,α^2-diol.

5. α^1-(cyclopentylaminomethyl)-4-hydroxy-*m*-xylene-α^1,α^2-diol.

6. 4-hydroxy-α^1-(1-isopropylaminopropyl)-*m*-xylene-$\alpha^1\alpha^2$-diol.

7. 4-hydroxy-α^1-[(2-indol-3-yl-1-methylethyl)amino]methyl-*m*-xylene-α^1,α^2-diol.

8. 4-hydroxy-α^1-{[(1-methyl-2-phenoxyethyl)amino]methyl} - *m* - xylene-α^1,α^2-diol.

9. 4-hydroxy-α^1-{[(*p*-methoxy-α-methylphenethyl)amino]methyl} - *m* - xylene-α^1,α^2-diol.

10. 5-(2-*tert.*-butylamino-1-hydroxyethyl)-salicylamide.

11. 5-(1-hydroxy-2-isopropylaminoethyl) salicylic acid methyl ester.

12. 5-(2-amino-1-hydroxyethyl)-salicylic acid methyl ester.

13. 5-(1-hydroxy-2-isopropylaminoethyl)-salicylamide.

14. 5-{1-Hydroxy-2-[(1-methyl-2-phenoxyethyl)amino]ethyl} salicylamide.

15. 5-(1-hydroxy-2-isopropylaminoethyl)-N-methyl salicylamide.

16. α^1-(benzyl-tert-butylaminomethyl)-4-hydroxy-*m*-xylene-α^1,α^2-diol.

17. N-benzyl-5-(1-hydroxy-2-isopropylaminoethyl) salicylamide.

18. 5-[1-hydroxy-2-(p-methoxy - α - methylphenethyl)aminoethyl] salicylic acid methyl ester.

19. 5-[1-hydroxy-2-(isopropylamino)-butyl] salicylamide.

20. 4[1-hydroxy-2-(isopropylamino)ethyl]salicylic acid methyl ester.

21. 4-hydroxy-α^1-[(p-hydroxy-α-methyl phenethyl amino)methyl] - *m* - xylene-α^1,α^2-diol.

22. 4-hydroxy-α^1-{[(1-methyl-2-morpholinoethyl)amino]methyl} - *m* - xylene-α^1,α^2-diol.

23. Physiologically acceptable acid addition salts of the compound claimed in any of claims 2 to 12.

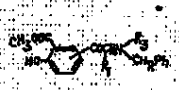
24. Compounds as claimed in claim 1 the preparation of which is specifically described in the Examples, excluding those claimed in claims 1 to 23.

25. A process for the preparation of compounds as claimed in claim 1 which comprises reducing the carbonyl group

of a ketone of the above general formula to an alcoholic group in which X, R_1, R_2 and R_3 have the meanings given in claim 1 or are convertible thereto, if desired with protection of the phenolic hydroxy group, the product if desired being isolated in the form of a physiologically acceptable acid addition salt.

26. A process as claimed in claim 25 in which the subsequent conversion is effected on compounds in which R_2 and R_3 both represent hydrogen or benzyl groups, and consists in reductive alkylation with an aldehyde or ketone in the presence of hydrogen and a noble metal catalyst.

27. A process as claimed in claim 25 in which the ketone is of the formula



and the reduction of the carbonyl group to the alcoholic group is effected with sodium borohydride, lithium aluminium hydride, or by catalytic hydrogenation, if desired with protection of the phenolic hydroxyl group with a benzyl ether or acetate group removable by hydrogenolysis or hydrolysis.

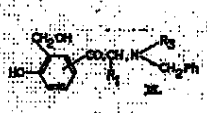
28. A process as claimed in claim 27 for the production of compounds in which R_2 and R_3 both represent hydrogen atoms in which a ketone of the formula given in claim 27 in which R_2 represents a benzyl radical is subjected to catalytic hydrogenation.

29. A process as claimed in claim 27 for the production of compounds as claimed in claim 1 in which X is an alkoxy carbonyl radical —$COOR_4$ in which R_4 has the meaning given in claim 1 which comprises reacting a ketone of the formula given in claim 27 in which X represents a —COOH group with an alcohol of the general formula R_4OH in the presence of an acid catalyst followed by catalytic hydrogenolysis.

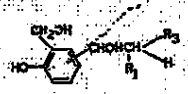
30. A process as claimed in claim 25 for the production of compounds in which X is a hydroxymethyl group which comprises reducing a compound of the formula given in that claim in which X is an ester group —COOMe with subsequent catalytic hydrogenolysis.

31. A process as claimed in claim 30 in which the reduction of the ester group is effected with lithium aluminium hydride and hydrogenolysis of the resultant —CH_2OH group during subsequent reduction is minimised by the addition of a volatile base to the reaction mixture.

32. A process as claimed in claim 25 which comprises subjecting a compound of the formula



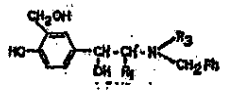
to catalytic hydrogenation to yield a compound of the formula



in which R and R_3 have the meanings given in claim 1.

33. A process as claimed in claim 32 in which the reduction is effected with palladised charcoal.

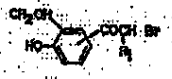
34. A modification of the process claimed in claim 32 in which the ketone of formula III is reduced to the alcohol of the formula



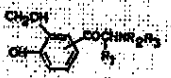
which may if desired by subjected to catalytic hydrogenation to remove the N-benzyl group.

35. A process as claimed in claim 34 in which the reduction is effected with sodium borohydride.

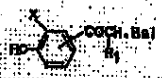
36. A process as claimed in claim 25 in which the ketone is prepared by the reaction of a compound of the formula:



where the OH groups may be protected (in which R_1 has the meaning given in claim 1) with an amine of the formula R_2R_3NH (in which R_2 and R_3 have the meaning given in claim 1) to produce a compound of the formula



37. A process as claimed in claim 25 in which the ketone is prepared by the reaction of a compound of the formula



with an amine of the formula R_2R_3NH (in which X, Hal, R_1, R_2, and R_3 have the meanings given in claim 1).

38. A process as claimed in claim 25 for the preparation of compounds in which X represents —COOH which comprises hydrolysing the corresponding ketone in which X represents the group COOMe and then reducing the ketone to the alcohol.

39. A process as claimed in claim 25 for the production of compounds in which X represents $—CONR_4R_5$ in which R_4 and R_5 have the meanings given in claim 1 which comprises reacting the corresponding ketone in which X represents the group $COOR_4$ in which R_4 has the meaning given in claim 1 with an amine of the formula NHR_4R_5 and reducing the resulting ketone to the alcohol.

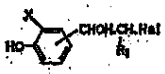
40. A modification of the process claimed in claim 39 in which an alcohol of the formula

is reacted with an amine of the formula NHR_6R_7 (in which R_6 and R_7 have the meanings given in claim 1).

41. A process as claimed in claim 25 for the production of compounds in which X is CONHOH or $CONHNH_2$ which comprises reducing the corresponding ketone in which X represents the group $COOR_4$ to the alcohol and reacting this with hydroxylamine or hydrazine to effect conversion of the group $COOR_4$ to the group CONHOH or $CONHNH_2$.

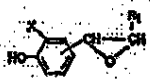
42. A modification of the process claimed in claim 25 for the production of compounds in which the group X represents a secondary or tertiary alcoholic group which comprises converting a compound of formula I in which the group X is replaced by a halogen atom to an organometallic compound and reaction of the resulting organometallic compound with an aldehyde or ketone.

43. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a halohydrin of the general formula



VIII

or an epoxide of the general formula



with an amine of the formula R_3R_4NH in which X, R_1, R_2, R_3 have the meanings given in claim 1 and Hal represents halogen.

44. A process for the preparation of compounds as claimed in claim 1 substantially as herein described with reference to Examples 1 to 39.

45. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 25 to 44.

46. Pharmaceutical compositions containing as active ingredients one or more compounds as claimed in claim 1 or claim 45 in association with a pharmaceutically acceptable carrier.

47. Pharmaceutical compositions as claimed in claim 46 adapted for oral administration, for administration by injection, or as suppositories or in a form suitable for inhalation.

48. Compositions as claimed in claim 47 in tablet form suitable for oral administration, if desired sub-lingually.

49. Compositions as claimed in claim 47 in the form of aerosol sprays.

50. Pharmaceutical compositions as claimed in claim 46 substantially as herein described with reference to Examples 40 to 44.

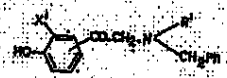
51. 1-phenyl-2-amino-ethanol derivatives of the general formula I

(I)

in which X' is a hydroxymethyl radical, or a radical of the general formula —COR'$_1$, in which R'$_1$ is a hydroxyl radical, or an alkoxy radical —OR'$_2$ in which R'$_2$ is a straight or branched chain alkyl group containing from 1 to 6 carbon atoms, or R'$_1$ is an —NHOH or an —NR'$_3$R'$_4$ radical, in which R'$_3$ and R'$_4$ may be the same or different, and are each a hydrogen atom or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms, or an aralkyl radical, or R'$_3$ and R'$_4$ together with the adjacent nitrogen atom, form a heterocyclic ring, which may contain additional hetero atoms, R' is a hydrogen atom, or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms, or a cycloalkyl radical or an aralkyl radical, or an aryloxyalkyl or 3-indolylalkyl radical, and physiologically acceptable acid addition salts thereof.

52. Pharmaceutical compositions containing as active ingredient one or more compounds as claimed in claim 51 together with a pharmaceutically acceptable carrier.

53. A process for the preparation of compounds as claimed in claim 51 which comprises converting the methoxycarbonyl group of the ketone of the general formula II (X' = CO_2Me)

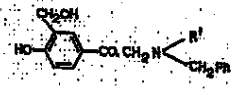


(II)

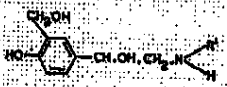
in which R′ has the meaning in claim 51, to any of the other radicals represented by X′ either directly, or after reduction of the carbonyl group to the alcohol with sodium borohydride, or by catalytic hydrogenation, the N-benzyl group being removed by catalytic hydrogenolysis when the carbonyl group, if still present, is reduced to the desired alcohol, and the product if desired being isolated as an acid addition salt.

54. Compounds as claimed in claim 51 when prepared by a process as claimed in claim 53.

55. A process for the preparation of compounds as claimed in claim 51 in which X′ is a hydroxymethyl group in which a compound of the formula



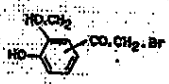
in which R′ has the meaning given in claim 51 is subjected to catalytic hydrogenation to yield a compound of the formula



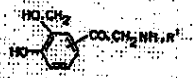
56. A process as claimed in claim 55 in which the hydrogenation is effected with a palladium charcoal catalyst.

57. Compounds as claimed in claim 51 in which X′ is hydroxymethyl when prepared by a process as claimed in claim 55 or claim 56.

58. A process for the preparation of compounds as claimed in claim 51 in which X′ represents a —CH_2OH group in which a compound of the formula



is condensed with a primary amine of the formula $R'NH_2$ in which R′ has the meaning given in claim 51 to produce a compound of the formula



which is then reduced.

59. Compounds as claimed in claim 51 when prepared by a process as claimed in claim 58.

ELKINGTON AND FIFE,
Chartered Patent Agents,
High Holborn House,
52/54 High Holborn,
London, W.C.1.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

EXHIBIT 4

PATENT SPECIFICATION (11) 1298494

1298494

NO DRAWINGS

(21) Application No. 29367/70 (22) Filed 17 June 1970

(23) Complete Specification filed 18 May 1971

(45) Complete Specification published 6 Dec. 1972

(51) International Classification C07C 91/34 101/72 A61K 27/00

(52) Index at acceptance

C2C 220 226 227 22Y 29X 29Y 302 30Y 322 323 32Y 360 361 362 364 365 366 368 36Y 456 45Y 503 509 50Y 620 623 624 628 650 652 65X 662 668 682 790 79Y LF LS

(72) Inventor DAVID MIDDLEMISS

(54) PHENYLETHANOLAMINE DERIVATIVES

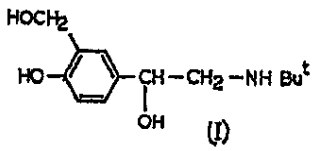
(71) We, ALLEN & HANBURYS LIMITED, a British Company of Three Colts Lane, Bethnal Green, London, E.2., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a process for the preparation of optical enantiomers of certain 1 - phenyl - 2 - aminoethanol derivatives which are described in particular in our United Kingdom Specification No. 1,200,886.

In our said United Kingdom Specification No. 1,200,886 there are described phenylaminoethanol derivatives which may stimulate β - adrenergic receptors e.g. α^1 - t - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol (I). The practical utility of such activity is more fully described in said Specification.

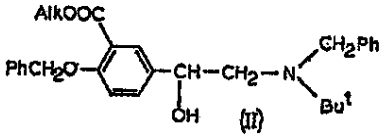
The phenylaminoethanol derivatives (I) may exist in two optically isomeric forms and according to the invention we have discovered a new process for the preparation of such isomers; the advantage of this process is that it facilitates the production of pure isomers. This is of particular importance in this case since the pharmacological activity of one isomer in standard tests for bronchodilator action is very much greater than that of the other.

The present invention therefore relates to a process for the preparation of optical enantiomers of α^1 - t - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol (I):



(I)

and physiologically acceptable acid addition salts thereof, which comprises treating a basic ester of the general formula II:



(II)

in which AlK represents a straight or branched chain alkyl radical containing 1 to 6 carbon atoms with an optically active form of di - p - toluoyl tartaric acid in an organic solvent, crystallising the product, isolating a selected crystalline fraction, and recovering from said fraction an optical enantiomer of formula II, whereafter the optical enantiomer of formula I is recovered either as such or in the form of an acid addition salt by removal of the protective benzyl groups, with previous, simultaneous or subsequent conversion of the —COOAlk group to a group —CH_2OH.

The organic solvent in which the optically active form of di - p - toluoyl tartaric acid is dissolved is preferably an organic ester, such as ethyl acetate. The group —COOAlk may be converted to the group —CH_2OH by reduction with a suitable metal hydride or complex metal hydride, e.g. lithium aluminium hydride whilst the protective benzyl groups may be removed by catalytic hydrogenolysis over a noble metal catalyst e.g. a palladium charcoal catalyst.

The R(−) isomer of (I) has been found to be approximately fifty times more active than the S(+) isomer in antagonising the increased bronchial resistance produced by administration of acetyl chlorine in the anaesthetised guinea-pig (Konzett-Rossler preparation). The isomers (as the acetate-monomethanolate) have the following physical characteristics:

	m.p.	$[\alpha]_D^{25}$	c(MeOH)
R(−) isomer	143.9°C	+36.9°	0.23
S(+) isomer	143.0°C	−36.9°	0.27

The isomers themselves have the following characteristics:

R(−) isomer	−26°	0.36
S(+) isomer	+25°	0.4

In a further aspect of the invention therefore there are provided optically isomeric forms of the compound of formula I and their salts. The invention also provides pharmaceutical compositions comprising said isomers or their salts.

The invention also extends to the optically pure methyl esters of formula II.

Such pharmaceutical compositions may include as carrier any material conventionally referred to as such and includes excipients and formulatory agents. The compositions may contain supplementary medicinal agents if desired. Suitable solid carriers include maize starch, calcium sulphate dihydrate, lactose etc.

The compositions may include for instance solid and liquid preparations for oral use, suppositories, injections, or forms suitable for administration by inhalation.

Oral administration is most convenient in the form of tablets which may be prepared according to conventional methods, and may be coated if required. Soluble tablets suitable for sublingual administration may also be used.

Injections may be formulated with the aid of physiologically acceptable carriers and agents as solutions, suspensions or as dry products for reconstitution before use.

For administration by inhalation the compositions according to the invention are conveniently in the form of an aerosol spray presentation.

The following Examples illustrate the invention: (in these Examples as elsewhere in the Specification the abbreviation *t* in relation to butyl means tertiary).

Example 1

Resolution of *dl* - 5 - (2 - Benzyl - *t* - butylamino - 1 - hydoxyethyl) - 2 - benzyloxybenzoic acid, methyl ester and conversion into the (+) and (−) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - α^1,α^3-diol

(−) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester.

A solution of the racemic base (30 g.) prepared by condensing methyl 2 - benzyloxy - 5 - bromoacetyl benzoate [see Collin et al, J. Med. Chem. *13* 674 (1970)] with *t* - butylbenzylamine in ethyl methyl ketone and reducing the crude product with sodium borohydride in ethanol by the general procedures already described in our United Kingdom Patent Specification No. 1,200,886 and (+) - O,O - di - *p* - toluoyltartaric acid (25.6 g.) in ethyl acetate (350 ml) at 70° was cooled slowly to room temperature and the precipitated salt was filtered off and dried (27 g., m.p. 130.0°, $[\alpha]_D^{25}$+49°, c=1, MeOH). Three recrystallisations from ethyl acetate gave material of constant rotation and melting point (m.p. 142.5° $[\alpha]_D^{25}$+47°, c=1.2, MeOH). This salt (10 g) in ethyl acetate was washed with sodium bicarbonate solution to remove the toluoyl tartaric acid.

The ethyl acetate was then evaporated and the residue recrystallised from petroleum ether (b.p. 40—60°C) to give the free base as colourless needles, (3 g, m.p. 87.0° $[\alpha]_D^{25}$−18.4, c=0.38, MeOH).

(+) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxybenzoic acid, methyl ester.

This material was isolated from a procedure similar to the above using (−) - O,O - di - *p* - toluoyl tartaric acid as the resolving agent. Thus a solution of the racemic base (30 g) and (−) - O,O - di - *p* - toluoyl tartaric acid (25.6 g) in ethyl acetate (350 ml) deposited a salt, (27 g. m.p. 134—5° $[\alpha]_D^{25}$−48°, c=1, MeOH). Three recrystallisations from ethyl acetate gave material with constent m.p. 141.5° and $[\alpha]_D^{25}$−47°, c=1.5, MeOH. This salt (11 g) in ethyl acetate was converted into the *free base*, by extraction of the (−) - O,O - di - *p* - toluoyl tartaric acid with sodium bicarbonate solution. The ethyl acetate was removed and the residue recrystallised from petroleum ether (b.p. 40—60°) to give the free base (4.5 g., mp 87.0° $[\alpha]_D^{25}$+18.3, c=0.35, MeOH).

(+) - α^1 - *t* - Butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol acetate

A solution of (−) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester (2.5 g) in dry tetrahydrofuran was added during 5 minutes to a stirred suspension of lithium aluminium hydride (0.5 g) in dry tetrahydrofuran (50 ml) and the mixture was heated to reflux and then allowed to cool. Excess hydride was decomposed with water and the product extracted with ether. Evaporation of the ether gave α^1 - benzyl - *t* - butylaminomethyl - 4 - benzyloxy - m - xylene - α^1,α^3 - diol (2.1 g) as a colourless oil that was hydrogenated (50 ml) in the presence of 10%

palladium on carbon (0.7 g) until uptake ceased. Removal of the catalyst and solvent gave (+) - α^1 - t - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol as a colourless gum ($[\alpha]_D^{24}$+25°, c=0.4, MeOH). This was converted into a crystalline acetate salt (m.p. 143.0°, $[\alpha]_D^{28}$+36.9°, c=0.23, MeOH (from methanolether). Analysis of this salt confirmed the presence of one molecule of methanol of crystallisation.

(−) - α^1 - t - Butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol acetate

In a manner similar to that above (+) - 5(2 - benzyl - t - butylamino - 1 - hydroxyethyl) - 2 - benzyloxybenzoic acid, methyl ester was reduced with lithium aluminium hydride and then hydrogenated to give (−) - α^1 - t - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol ($[\alpha]_D^{24}$−26°, c=0.36, MeOH). The acetate salt monomethanolate had mp 143.9°, $[\alpha]_D^{23}$−36.9°, c=0.27, MeOH.

The following are Examples of pharmaceutical compositions containing isomers or their salts according to the invention. In each case the term active ingredient means one of the two isomers or their salts prepared according to Example I.

Example 2

Tablets suitable for oral administration.

Formula	1 mg Tablet	10,000 Tablets.
active ingredient	1.2 mg	12.0 g
calcium sulphate dihydrate	88.2 mg	882.0 g
maize starch	24.0 mg	240.0 g
Amijel	6.0 mg	60.0 g
magnesium stearate	0.6 mg	6.0 g
	120.0 mg	1200.0 g

Method

1. All the ingredients except the magnesium stearate, are mixed together, the mixed powders are graulated with water, and the damp mass is passed through a 16 mesh screen.
2. The wet granules are dried, and then passed through a 20 mesh screen.
3. The dried granules and the magnesium stearate are mixed together and compressed on a suitable tablet machine fitted with ¼" normal convave punches, to produce the required tablets.

Example 3

An aerosol formulation, expressed in terms of a single metered dose.

Formula	100 μg dose
active ingredient	100 μg
oleic acid	10 μg
dichlorodifluoromethane	61 mg
trichlorofluoromethane	24 mg

Method

The active ingredient, the oleic acid and part of the trichlorofluoromethane are mixed together. The suspension is then diluted with the remainder of the trichlorofluoromethane, and the requisite quantity is filled into aluminium aerosol containers which are closed by a suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

Example 4

Formula	100 μg dose
active ingredient	120 μg
sorbitan Trioleate	120 μg
Dichlorodifluoromethane B.P.C.	61 mg
Trichlorofluoromethane B.P.C.	24 mg

Method

Mix together the active ingredient, sorbitan trioleate, and part of the trichlorofluoromethane. The suspension is then diluted with the remainder of the trichlorofluoromethane and the requisite quantity of filled into aluminium aerosol containers, which are closed by a suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

Example 5

Formula	100 μg dose
active ingredient	120 μg
2-dimethylaminoethanol	26.6 μg
Oleic acid B. P. 1963	93.4 μg
Dichlorodifluoromethane B.P.C.	61 mg
Trichlorofluoromethane B.P.C.	24 mg

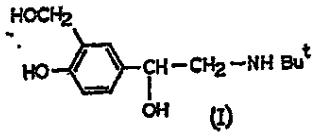
Method

The active ingredient, the oleic acid, 2 - dimethylaminoethanol and part of the trichlorofluoromethane are mixed together. The suspension is then diluted with the remainder of the trichlorofluoromethane, and the requisite quantity is filled into aluminium aerosol containers, which are closed by a

suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

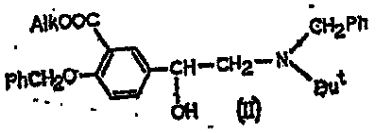
WHAT WE CLAIM IS:—

1. A process for the preparation of optical enantiomers of α^1 - *t* - butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol (I):



(I)

and physiologically acceptable acid addition salts thereof, which comprises treating a basic ester of the general formula II:



(II)

in which Alk represents a straight or branched chain alkyl radical containing 1 to 6 carbon atoms with an optically active form of di - p - toluoyl tartaric acid in an organic solvent, crystallising the product, isolating a selected crystalline fraction, and recovering from said fraction an optical enantiomer of formula II, whereafter the optical enantiomer of formula I is recovered either as such or in the form of an acid addition salt by removal of the protective benzyl groups, with previous, simultaneous or subsequent conversion of the —COOAlk group to a group —CH_2OH.

2. A process as claimed in claim 1 in which the organic solvent used for the resolving acid is an organic ester.

3. A process as claimed in claim 2 in which the solvent is ethyl acetate.

4. A process as claimed in any of claims 1 to 3 for the production of compounds of formula I in which prior to the removal of the protective groups, the COOAlk group is converted to a group —CH_2OH by reduction with lithium aluminium hydride, and in which the protective groups are then removed by catalytic hydrogenolysis with a palladium charcoal catalyst.

5. A process as claimed in claim 4 for the production of the (+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol, which comprises preparing the salt of (+) - O,O - di - *p* - toluoyl tartaric acid and the *dl* racemate of 5(2 - benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester in an organic solvent, recovering a selected salt of constant rotation by fractional crystallisation, decomposing said salt to recover (—) isomer of the ester, reducing said ester with lithium aluminium hydride and hydrogenating the product using a palladium charcoal catalyst.

6. A process as claimed in claim 4 for the production of the (—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene α^1,α^3 - diol, which comprises preparing the salt of (—) - O,O - di - *p* - toluoyl tartaric acid and the *dl* racemate of 5(2 - benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester in an organic solvent, recovering a selected salt of constant rotation by fractional crystallisation, decomposing said salt to recover the (+) isomer of the ester, reducing said ester with lithium aluminium hydride and hydrogenating the product using a palladium charcoal catalyst.

7. A process as claimed in claim 1 substantially as herein described with reference to Example 1.

8. Optical enantiomers of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol and physiologically acceptable acid addition salts thereof when prepared by a process as claimed in any of claims 1 to 7.

9. The R(—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol in the form of the acetate monomethanolate having m.p. - 143.9°C and $[\alpha]_D^{23}$—36.9°, c (MeOH)=0.27.

10. The S(+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol in the form of the acetate monomethanolate having m.p. 143.0°C and $[\alpha]_D^{23}$+36.9°, c (MeOH)=0.23.

11. The R(—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol having $[\alpha]_D^{24}$—26°, c=0.36 MeOH.

12. The S(+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol having $[\alpha]_D^{24}$+25°, c=0.4 MeOH.

13. A pharmaceutical composition comprising as active ingredient or as one such ingredient an optical enantiomer as claimed in claim 8 in association with a non-toxic pharmaceutical carrier.

14. A composition as claimed in claim 13 adapted for oral use.

15. A composition as claimed in claim 13 adapted for parenteral administration.

16. A composition as claimed in claim 13 adapted for inhalation.

17. Compositions as claimed in any of claims 13 to 16 in which the active ingredient is or includes the acetate monomethanolate denfied in claim 9 or claim 10.

18. Compositions as claimed in any of

claims 13 to 16 in which the active ingredient is or includes the diol defined in claim 11 or 12.

19. Compositions as claimed in claim 13 substantially as herein described with reference to any one of Examples 2 to 5.

20. (—) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester, m.p. 87.0°C, $[\alpha]_D^{23}$ — 18.4, c=0.28, MeOH.

21. (+) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester m.p. 87.0°C. $[\alpha]_D^{23}$ + 18.3, c=0.35 MeOH.

ELKINGTON & FIFE,
Chartered Patent Agents,
High Holborn House,
52/54 High Holborn,
London, WC1V 6SH.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.